



**Linea guida pubblicata nel Sistema Nazionale Linee Guida**  
**Roma, 15 marzo 2024**

**LINEE GUIDA PER LO SCREENING E LA DIAGNOSI DEL TUMORE DELLA MAMMELLA  
(ADOLOPMENT LINEE GUIDA EUROPEE): RACCOMANDAZIONI SECONDO LIVELLO,  
STAGING E PIANIFICAZIONE PRE-OPERATORIA**

**Società Scientifiche coinvolte**

<b>AIOM</b>	Associazione Italiana di Oncologia Medica
<b>AIRO</b>	Associazione Italiana di Radioterapia e Oncologia Clinica
<b>SIAPEC-IAP</b>	Società Italiana di Anatomia Patologica e Citologia Diagnostica Divisione italiana della International Academy of Pathology
<b>SICPRE</b>	Società Italiana di chirurgia plastica ricostruttiva ed estetica
<b>SIRM</b>	Società Italiana di Radiologia Medica ed Interventistica
<b>AIE</b>	Associazione Italiana di Epidemiologia
<b>AIFM</b>	Associazione Italiana di Fisica Medica
<b>SITI</b>	Società Italiana di Igiene Medicina Preventiva e Sanità Pubblica
<b>FASTeR</b>	Federazione delle Associazioni Scientifiche dei Tecnici di Radiologia
<b>AIMN</b>	Associazione Italiana di Medicina Nucleare
<b>SICi</b>	Società Italiana di Citologia

**Comitato Tecnico Scientifico (CTS)**

1. Cannatà Vittorio (AIFM) Fisico medico, Responsabile Servizio Fisica Sanitaria IRCCS Ospedale Pediatrico Bambino Gesù - Roma
2. Castellano Isabella (SIAPEC) Anatomo patologo, Dipartimento di Scienze Mediche Università di Torino
3. Dardanoni Gabriella (AIE), Medico epidemiologo, Palermo
4. Francolini Giulio (AIRO) Oncologo radioterapista, Azienda Ospedaliero Univarsitaria Careggi - Firenze
5. Gori Stefania (AIOM), Oncologo, Direttore Oncologia Medica - Direttore Dipartimento Oncologico - IRCCS Ospedale Sacro Cuore Don Calabria, Negrar di Valpolicella
6. Magliocca Carlo (SICPRE) Chirurgo plastico, Ospedale Fatebenefratelli – Isola Tiberina, Roma

7. Montemezzi Stefania (SIRM) Radiologo, Direttore U.O.C. di Radiologia BT  
Direttore DAI Patologia e Diagnostica  
Azienda Ospedaliera Universitaria Integrata - Verona
8. Pacifici Stefano (FASTER/AITERS) Tecnico Sanitario di radiologia medica (TSRM), Unicamillus  
International Medical University - Roma
9. Torri Emanuele (SITI) Dirigente Medico di Sanità pubblica, presso Provincia autonoma di Trento
10. Trianni Annalisa (AIFM) Fisico, specializzato in fisica sanitaria, Direttore UO di fisica Sanitaria  
dell'Azienda Provinciale per i servizi sanitari di Trento (Apss)
11. Pellegrini Antonella (SICi) Dirigente Biologo, Citologia Diagnostica, AO S. Giovanni-Addolorata,  
Roma

### **Gruppo di Lavoro metodologico**

1. Battisti Francesca, Istituto lo studio la prevenzione e la rete oncologica (ISPRO) Firenze
2. Deandrea Silvia, (ATS della Provincia di Pavia, DG Welfare Regione Lombardia)
3. Ferretti Stefano, Dip. Medicina Traslazionale e per la Romagna, Università di Ferrara Registro  
Tumori della Regione Emilia-Romagna, Unità funzionale Azienda USL Ferrara
4. Giordano Livia, CPO Piemonte Città della Salute e della Scienza, TORINO
5. Giorgi Rossi Paolo, Azienda Unità Sanitaria Locale, IRCCS di Reggio Emilia
6. Mantellini Paola, Istituto lo studio la prevenzione e la rete oncologica (ISPRO) Firenze
7. Paci Eugenio, Medico epidemiologo, Firenze
8. Parmelli Elena, JRC-ISPRA
9. Rossi Martina, Istituto lo studio la prevenzione e la rete oncologica (ISPRO), Firenze
10. Zappa Marco, Medico epidemiologo, Firenze

Al fine di facilitare il processo di votazione si è costituito un **Panel mobile**, ovvero un sottogruppo di esperti già appartenenti al Panel che ha espresso interesse alla partecipazione attiva alle plenarie e conseguenti votazioni. Il panel è stato creato su adesione volontaria dei seguenti esperti in materia:

### **Membri del panel mobile**

Daniela Ambrogetti	Radiologa, ISPRO, Firenze
Catia Angiolini	Oncologa, Azienda Ospedaliero Universitaria Careggi, Firenze
Adriana Bonifacino	Presidente IncontraDonna - Responsabile Senologia Clinica e Diagnostica IDI - IRCCS Roma
Laura Bonvicini	Epidemiologa, Azienda Usl, Reggio Emilia
Beniamino Brancato	Radiologo senologo, ISPRO, Firenze
Capobussi Matteo	Medico epidemiologo, MMG convenzionato con il SSN – ATS Brianza Metodologo, vice co-chair

Francesca Caumo	Radiologa/senologa, Istituto Oncologico Veneto IOV – IRCCS, Padova, Italia
Leopoldo Costarelli	Dirigente medico della UOC Anatomia Patologica dell’Azienda Ospedaliera S. Giovanni-Addolorata – Roma
Silvia Deandrea	Metodologa, co-chair, - ATS della Provincia di Pavia, DG Welfare Regione Lombardia
Flori Degrassi	Presidente ANDOS Nazionale
Prassede Foxi	Dirigente Biologo, Presidio Ospedaliero di Pescia (Azienda USL Toscana Centro) SOC Anatomia Patologica Pistoia – Pescia
Livia Giordano	Medico epidemiologo, CPO Piemonte Città della Salute e della Scienza, Torino
Paolo Giorgi Rossi	Epidemiologo, Azienda Unità Sanitaria Locale, IRCCS di Reggio Emilia
Icro Meattini	Radioterapista, Dipartimento di Scienze Biomediche Sperimentali e Cliniche "M. Serio" - Università di Firenze - Radioterapia Oncologica, Dipartimento di Oncologia - Azienda Ospedaliero Universitaria Careggi (AOUC), Firenze
Eugenio Paci	Medico epidemiologo, Firenze
Francesca Pietribiasi	Medico Patologo, vice co-chair, ASL TO5 - Ospedale S. Croce, Moncalieri (TO)
Santinelli Alfredo	Direttore UOC di Anatomia Patologica – Azienda Ospedaliera “Ospedali Riuniti Marche Nord”, Pesaro
Carlo Senore	Medico Epidemiologo, vice co-chair. Epidemiologo, CPO Piemonte Città della Salute e della Scienza, Torino
Marco Zappa	Medico epidemiologo, Firenze

### **Revisori esterni indipendenti**

Antonio Rizzo - patologo	Humanitas Catania
Rubina Trimboli - radiologa	Humanitas Milano
Marco Lucioni – patologo	Università di Pavia

## INDICE

SINOSSI RACCOMANDAZIONI	pag. 5
Raccomandazioni approfondimento diagnostico	pag. 9
Raccomandazioni planning pre-operatorio	pag. 9
Raccomandazioni staging	pag. 9
Raccomandazioni pianificazione terapia	pag. 9
1. Introduzione razionale	pag. 10
2. Obiettivo	pag. 10
3. Metodologia	pag. 11
3.1 La governance del processo	pag. 11
3.2 Scoping delle linee guida	pag. 12
3.3 Tempi e organizzazione del lavoro	pag. 13
3.4 Temi che ricadono nello scope delle Linee Guida Europee	pag. 13
3.5 Formato previsto delle linee guida finali	pag. 16
3.6 Modalità di comunicazione ad interim e finale	pag. 16
3.7 Prospettive per lo sviluppo di un “percorso donna”	pag. 16
4. Revisione esterna	pag. 17
5. Applicabilità	pag. 17
6. Aggiornamento della LG: tempi e modalità	pag. 17
7. Conflitti di interesse editoriale	pag. 17
Bibliografia	pag. 18
Flow-chart 1	pag. 19
Flow-chart 2	pag. 20
Regole per il panel	pag. 21
ETD	pag. 24
Quesito 1	pag. 24
Quesito 2	pag. 44
Quesito 3	pag. 60

Quesito 4	pag. 63
Quesito 5	pag. 67
Quesito 6	pag. 81
Quesito 7	pag. 85
Quesito 8	pag. 103
Quesito 9	pag. 106
Quesito 10	pag. 110
Quesito 11	pag. 113
Quesito 12	pag. 131
Quesito 13	pag. 150
Quesito 14	pag. 169
Quesito 15	pag. 172
Revisioni esterne	pag. 176

## SINOSI RACCOMANDAZIONI

**Quesito 1** *Dovrebbe risonanza magnetica aggiuntiva vs nessuna risonanza magnetica aggiuntiva essere utilizzato per donne con conferma istologica di carcinoma duttale in situ per il planning preoperatorio?*

**Raccomandazione:** Nelle donne con carcinoma duttale in situ confermato (DCIS), il panel suggerisce di non utilizzare una risonanza magnetica addizionale per il planning preoperatorio (raccomandazione su condizione, certezza delle evidenze molto bassa). **Raccomandazione su condizione contro l'intervento.**

**Quesito 2** *Dovrebbe CESM o CEM vs. risonanza magnetica essere utilizzato per diagnosticare donne con cancro alla mammella istologicamente invasivo in aiutare la scelta del trattamento chirurgico?*

**Raccomandazione:** Nelle donne con cancro della mammella invasivo istologicamente confermato, il panel suggerisce di utilizzare la CESM rispetto alla risonanza magnetica a supporto del planning del trattamento (raccomandazione su condizione, bassa certezza nelle evidenze di accuratezza). **Raccomandazione su condizione a favore dell'intervento.**

**Quesito 3** *Dovrebbe tomosintesi digitale della mammella vs. mammografia diagnostica essere utilizzato per diagnosticare cancro della mammella in donne richiamate per lesioni sospette alla mammografia di screening?*

**Raccomandazione:** Il panel suggerisce di utilizzare la tomosintesi rispetto alle proiezioni aggiuntive mammografiche nelle donne a medio rischio di cancro della mammella richiamate ad approfondimento per sospetto alla mammografia di screening (raccomandazione su condizione, certezza moderata delle evidenze di accuratezza). **Raccomandazione su condizione a favore dell'intervento.**

**Quesito 4** *Dovrebbe agobiopsia mammaria vs. citologia da aspirato ad ago sottile essere utilizzato per diagnosticare cancro della mammella in donne con lesioni sospette alla mammografia?*

**Raccomandazione:** Negli individui con lesioni della mammella sospette (tra cui masse, densità asimmetriche, calcificazioni e/o distorsioni architetturali) alla mammografia, il panel raccomanda la core biopsy invece della citologia ad ago sottile per la diagnosi di cancro della mammella (raccomandazione forte, certezza moderata nelle evidenze). **Raccomandazione forte a favore dell'intervento.**

**Quesito 5** *Dovrebbe agobiopsia a guida stereotassica o VABB a guida stereotassica vs. agobiopsia ecoguidata o VABB ecoguidata essere utilizzato per diagnosticare la presenza del cancro alla mammella in donne positive per calcificazioni al seno?*

**Raccomandazione:** Nelle donne che si presentano con calcificazioni, il panel raccomanda l'uso della core biopsy a guida stereotattica rispetto a quella a guida ecografica per la diagnosi di cancro della mammella (raccomandazione forte, bassa certezza nelle evidenze). **Raccomandazione forte a favore dell'intervento.**

**Quesito 6** *Dovrebbe posizionamento di clip vs nessuna clip dopo agobiopsia (NCB)/ agobiopsia vacuum assisted (VANCB) essere utilizzato per la scelta della terapia chirurgica in pazienti con cancro della mammella?*

**Raccomandazione:** Il panel suggerisce l'utilizzo del clip-marking dopo NCB/VANCB per il planning chirurgico in pazienti con cancro della mammella (raccomandazione su condizione, certezza molto bassa nelle evidenze). **Raccomandazione su condizione a favore dell'intervento.**

**Quesito 7** *Dovrebbe esami convenzionali per la stadiazione vs nessun esame essere utilizzato per pazienti con cancro alla mammella al primo stadio senza segni suggestivi per metastasi?*

**Raccomandazione:** Il panel suggerisce di non utilizzare esami di stadiazione con imaging nelle donne con cancro della mammella in stadio I (raccomandazione su condizione, bassa certezza delle evidenze)

**Raccomandazione su condizione contro l'intervento.**

**Quesito 8** *Dovrebbe Esami di stadiazione con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio I senza sintomi suggestivi di metastasi?*

**Raccomandazione:** Per le pazienti con cancro della mammella allo stadio I senza sintomi suggestivi per metastasi, il panel raccomanda di non utilizzare la PET-CT per la stadiazione (raccomandazione forte, certezza nelle evidenze molto bassa). **Raccomandazione forte contro l'intervento.**

**Quesito 9** *Dovrebbe esami convenzionali per la stadiazione vs nessun esame per la stadiazione essere utilizzato per pazienti con cancro alla mammella al secondo stadio senza segni suggestivi per metastasi*

**Raccomandazione:** Il panel suggerisce di non utilizzare esami di stadiazione con imaging nelle donne con cancro della mammella in stadio IIa e IIb (raccomandazione su condizione, bassa certezza delle evidenze).

**Raccomandazione su condizione contro l'intervento.**

**Quesito 10** *Dovrebbe esami di stadiazione con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio II senza sintomi suggestivi di metastasi*

**Raccomandazione:** Per i pazienti con stadio clinico IIa/IIb senza sintomi suggestivi per metastasi, il panel suggerisce di non utilizzare la PET-CT per la stadiazione (raccomandazione su condizione, certezza nelle evidenze molto bassa). **Raccomandazione su condizione contro l'intervento.**

**Quesito 11** *Dovrebbe esami convenzionali per la stadiazione vs nessun esame essere utilizzato per pazienti con cancro alla mammella al terzo stadio senza segni suggestivi per metastasi*

**Raccomandazione:** Il panel raccomanda di utilizzare esami di stadiazione convenzionali nelle donne con cancro della mammella in stadio III (raccomandazione forte, moderata certezza delle evidenze).

**Raccomandazione forte a favore dell'intervento.**

**Quesito 12** *Dovrebbe esami con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio III senza sintomi suggestivi di metastasi*

**Raccomandazione:** Per pazienti con cancro della mammella in stadio III senza sintomi suggestivi di metastasi, il panel suggerisce l'utilizzo della PET-CT rispetto allo staging convenzionale (raccomandazione su condizione, bassa certezza nelle evidenze). **Raccomandazione su condizione a favore dell'intervento.**

**Quesito 13** *Dovrebbe esami di stadiazione convenzionali seguiti da 18F-FDG PET-CT vs esami di stadiazione convenzionali essere utilizzato per pazienti con cancro della mammella clinicamente allo stadio III senza segni suggestivi di metastasi*



**Raccomandazione:** Per pazienti con cancro della mammella in stadio III senza sintomi suggestivi di metastasi, il panel suggerisce l'utilizzo di esami convenzionali di staging seguiti da PET-CT rispetto allo staging convenzionale da solo (raccomandazione su condizione, bassa certezza nelle evidenze).

**Raccomandazione su condizione a favore dell'intervento.**

**Quesito 14** *Dovrebbe una soglia del 10% o più vs 1% o più cellule positive per il recettore degli estrogeni essere utilizzato per utilizzare la terapia endocrina in donne con cancro invasivo alla mammella*

**Raccomandazione:** Nelle donne con cancro della mammella invasivo, il panel suggerisce la somministrazione di terapia endocrina adiuvante se l'1% o più delle cellule tumorali mostra positività agli estrogeni, rispetto ad utilizzare il 10% come criterio (raccomandazione su condizione, certezza molto bassa nelle evidenze).

**Raccomandazione su condizione contro l'intervento.**

**Quesito 15** *Dovrebbe una soglia del 10% o più vs 1% o più cellule positive per il recettore del progesterone essere utilizzato per utilizzare la terapia endocrina in donne con cancro invasivo alla mammella*

**Raccomandazione:** Nelle donne con cancro della mammella invasivo, il panel suggerisce la somministrazione di terapia endocrina adiuvante se l'1% o più delle cellule tumorali mostra positività al recettore del progesterone, rispetto ad utilizzare il 10% come criterio (raccomandazione su condizione, certezza molto bassa nelle evidenze). **Raccomandazione su condizione contro l'intervento.**

	<b>Adattata</b>	<b>Adottata</b>
<b>Quesito 1</b>	<b>X</b>	
<b>Quesito 2</b>	<b>X</b>	
<b>Quesito 3</b>		<b>X</b>
<b>Quesito 4</b>		<b>X</b>
<b>Quesito 5</b>		<b>X</b>
<b>Quesito 6</b>		<b>X</b>
<b>Quesito 7</b>	<b>X</b>	
<b>Quesito 8</b>		<b>X</b>
<b>Quesito 9</b>		<b>X</b>
<b>Quesito 10</b>		<b>X</b>
<b>Quesito 11</b>	<b>X</b>	
<b>Quesito 12</b>	<b>X</b>	
<b>Quesito 13</b>	<b>X</b>	
<b>Quesito 14</b>		<b>X</b>
<b>Quesito 15</b>		<b>X</b>

## **RACCOMANDAZIONI APPROFONDIMENTO DIAGNOSTICO**

Il panel suggerisce di utilizzare la tomosintesi rispetto alle proiezioni aggiuntive mammografiche nelle donne a medio rischio di cancro della mammella richiamate ad approfondimento per sospetto alla mammografia di screening.

Negli individui con lesioni della mammella sospette (tra cui masse, densità asimmetriche, calcificazioni e/o distorsioni architetturali) alla mammografia, il panel raccomanda la core biopsy invece della citologia ad ago sottile per la diagnosi di cancro della mammella

Nelle donne che si presentano con calcificazioni, il panel raccomanda l'uso della core biopsy a guida stereotattica rispetto a quella a guida ecografica per la diagnosi di cancro della mammella

## **RACCOMANDAZIONI PLANNING PRE-OPERATORIO**

Il panel suggerisce l'utilizzo del clip-marking dopo NCB/VANCB per il planning chirurgico in pazienti con cancro della mammella

Nelle donne con carcinoma duttale in situ confermato (DCIS), il panel suggerisce di non utilizzare una risonanza magnetica addizionale per il planning preoperatorio

Nelle donne con cancro della mammella invasivo istologicamente confermato, il panel suggerisce di utilizzare la CEMM rispetto alla risonanza magnetica a supporto del planning del trattamento

## **RACCOMANDAZIONI STAGING**

Per le donne con cancro della mammella in stadio:

I, IIa e IIb senza segni suggestivi di metastasi: il panel suggerisce di non utilizzare esami di stadiazione con imaging e di non utilizzare la PET-CT per la stadiazione III senza segni suggestivi per metastasi: il panel raccomanda di utilizzare esami di stadiazione convenzionali, suggerisce l'utilizzo della PET-CT rispetto allo staging convenzionale e suggerisce l'utilizzo di esami convenzionali di staging seguiti da PET-CT rispetto allo staging convenzionale da solo

## **RACCOMANDAZIONI PIANIFICAZIONE TERAPIA**

Nelle donne con cancro della mammella invasivo, il panel suggerisce la somministrazione di terapia endocrina adiuvante:

- se l'1% o più delle cellule tumorali mostra positività agli estrogeni, rispetto ad utilizzare il 10% come criterio
- se l'1% o più delle cellule tumorali mostra positività al recettore del progesterone, rispetto ad utilizzare il 10% come criterio

# **METODI DI LAVORO PER LE LINEE GUIDA ITALIANE PER LO SCREENING E LA DIAGNOSI DEL CANCRO DELLA MAMMELLA (ADOLOPMENT DELLE LINEE GUIDA EUROPEE)**

## **Introduzione**

### **1. Introduzione e Razionale**

Il panel ha deliberato 15 raccomandazioni: 13 discusse per esteso e 2 determinate logicamente sulla base delle altre raccomandazioni. L'attività si è svolta secondo le procedure descritte nei documenti "Metodi di lavoro per le linee guida italiane per lo screening e la diagnosi del cancro della mammella" e "Regole per il panel delle linee guida italiane per lo screening e la diagnosi del cancro della mammella"; il numero di plenarie del panel è stato pari a 5 e si sono svolte tutte in modalità da remoto.

Le Linee guida europee sullo screening mammografico (1) esistono da oltre 20 anni e forniscono agli Stati Membri le indicazioni per l'organizzazione dei programmi di screening, come richiesto dalla Raccomandazione del Consiglio dell'Unione europea del 2 dicembre 2003. A partire dal 2016, le raccomandazioni (*European Breast Cancer Guidelines on Screening and Diagnosis* – in seguito Linee Guida Europee) (2) sono sviluppate con il metodo GRADE (Grading of Recommendations Assessment, Development and Evaluation) e il framework GRADE Evidence to Decision (EtD) (3), lo stesso richiesto dal Sistema Nazionale Linee Guida (SNLG) per l'accettazione di linee guida nel sistema previsto dalla legge 24/2017 ("Legge Gelli").

Quindi, considerata la disponibilità di linee guida di riferimento dal punto di vista istituzionale e comunitario che presentano anche le caratteristiche richieste per l'inclusione nel sistema italiano, e la contestuale assenza di documenti analoghi sviluppati a livello nazionale, si è ritenuto utile attivare un processo di adozione e adattamento attraverso una procedura di adolopment (4), così come raccomandato dal Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure (CNEC) (5).

### **Obiettivo**

Il progetto si pone l'obiettivo finale di migliorare la qualità dello screening mammografico organizzato in Italia favorendo l'erogazione di attività clinica in accordo alle migliori evidenze. Per ottenere questo risultato è necessario favorire l'adozione e l'implementazione delle raccomandazioni delle linee guida nei programmi di screening italiani, sia a livello di politiche regionali sia a livello di prassi nelle realtà locali, attraverso la diffusione istituzionale di raccomandazioni adattate o adottate dalle Linee Guida Europee, o sviluppate de-novo con la stessa metodologia, in coerenza con l'assetto metodologico e istituzionale di SNLG.

*Utilizzatori target:*

- Ministero della Salute
- Regioni
- Conferenza Stato-Regioni
- Coordinamento interregionale di prevenzione
- Aziende Sanitarie e Ospedaliere Universitarie
- Associazioni di cittadini e pazienti.

### **3. Metodologia**

#### **3.1 La *governance* del processo**

Il promotore dell'iniziativa è l'Osservatorio Nazionale Screening (ONS), la società scientifica referente è il Gruppo Italiano Screening Mammografico (GISMa). Il processo di adolopment si avvale di un Comitato Tecnico Scientifico (CTS) composto dalle seguenti società scientifiche:

- AIE Associazione Italiana di Epidemiologia
- AIOM Associazione Italiana di Oncologia Medica
- AIFM Associazione Italiana di Fisica Medica
- AIMN Associazione Italiana di Medicina Nucleare
- AIRO Associazione Italiana di Radioterapia e Oncologia Clinica
- FASTeR Federazione delle Associazioni Scientifiche dei Tecnici di Radiologia
- SIAPEC-IAP Società Italiana di Anatomia Patologica e Citologia Diagnostica (Divisione italiana della International Academy of Pathology)
- SICi Società Italiana di Citologia
- SICPRE Società Italiana di chirurgia plastica ricostruttiva ed estetica
- SIRM Società Italiana di Radiologia Medica ed Interventistica
- SITI Società Italiana di Igiene Medicina Preventiva e Sanità Pubblica

La composizione del CTS include tutte le società scientifiche accreditate dal Ministero, la cui area è interessata dalle raccomandazioni delle Linee Guida Europee, e che hanno aderito all'invito trasmesso ai rispettivi presidenti dall'ONS.

Ciascuna società scientifica ha nominato un proprio rappresentante nel CTS. Il CTS, in linea con quanto richiesto da SNLIG, ha contribuito alla definizione dell'ambito di interesse (*scope*) delle linee guida italiane e in funzione di questo ha nominato i membri del Panel, di cui supervisionerà le attività.

Il Panel è il gruppo consultivo indipendente, multidisciplinare e multiprofessionale, composto da esperti di contenuto e membri laici, che ha lo scopo principale di sviluppare le raccomandazioni della linea guida finale. Le regole di lavoro del panel sono riportate in dettaglio in un documento specifico.

Il CTS e il Panel si avvalgono del supporto di un gruppo di coordinamento ed indirizzo, composto da rappresentanti dell'ONS, del GISMa ed esperti coinvolti nello sviluppo delle Linee Guida Europee, che ha la finalità di coordinare ed organizzare le sessioni di lavoro, così come di contribuire alla redazione dei documenti finali, dei verbali e delle varie rendicontazioni. È cura del CTS, supportato dal gruppo di coordinamento e indirizzo, definire le regole a cui il Panel deve attenersi nel percorso di adolopment monitorandone l'aderenza.

### **3.2 Scoping delle linee guida**

Le Linee Guida Europee, cioè le linee guida di partenza per il processo di adolopment, sono composte da circa 74 raccomandazioni che coprono le seguenti aree/processi del percorso di diagnosi precoce del cancro della mammella:

- Modalità organizzative dei programmi di screening
- Test di primo livello (es. tipo di esame, frequenza, fascia di età)
- Test di secondo livello
- Diagnosi
- Stadiazione preoperatoria
- Modalità di informazione/invito ai programmi di screening e comunicazione dei risultati
- Formazione degli operatori

Dal punto di vista della prospettiva, le Linee Guida Europee adottano sia quella individuale sia quella di popolazione. Le popolazioni di interesse sono rappresentate dalle donne eleggibili per lo screening mammografico e le donne sottoposte ad approfondimento diagnostico, sia per sintomi, per invio dopo una valutazione del rischio o per richiamo da primo livello di screening. Sono esclusi gli individui di sesso maschile, le ricorrenze loco-regionali dopo diagnosi di cancro, il cancro metastatico, il percorso delle donne ad alto rischio, la prevenzione primaria se non come intervento all'interno di un programma di screening. Le linee guida includono sia il setting pubblico sia il setting privato.

Il CTS si è confrontato rispetto all'ambito di interesse (*scope*) delle linee guida candidate all'adoption per valutare se mantenere lo stesso interesse per le linee guida nazionali oppure evidenziare eventuali aree carenti o, al contrario, non prioritarie.

Le conclusioni rispetto allo *scope* delle linee guida italiane sono:

- si conferma la priorità per tutti i processi correlati alla diagnosi e allo screening del tumore della mammella.

Nei paragrafi successivi saranno presentate le modalità per l'inclusione delle raccomandazioni su screening e diagnosi.

### **3.3 Tempi e organizzazione del lavoro**

Tutti i PICO delle Linee Guida Europee verranno considerati per l'adozione o adattamento (v. paragrafo 6). Il CTS ha condiviso l'idea di affrontare inizialmente l'argomento fasce d'età ed intervalli e successivamente la personalizzazione dello screening. A seguire verranno valutate le raccomandazioni relative al secondo livello, valutazione e stadiazione preoperatoria e aspetti organizzativi, comunicazione e formazione.

La formulazione di PICO ex novo sugli argomenti non trattati dalle linee guida europee potrà procedere parallelamente, ma la revisione della letteratura e il percorso di formulazione delle raccomandazioni sarà successivo all'adoption. Il CTS valuterà la proposta di uno o più PICO inerenti al percorso di diagnosi precoce delle neoplasie della mammella per le donne portatrici di protesi (estetica o ricostruttiva) dopo avere valutato i contenuti delle linee di indirizzo prodotte dal progetto FOCUS ON di Senonetwork.

### **3.4 Temi che ricadono nello *scope* delle Linee Guida Europee**

*Adozione o adattamento delle raccomandazioni*

Le raccomandazioni delle *Linee Guida Europee* possono essere “adottate” oppure “adattate”:

- **adozione:** la direzione e la forza della raccomandazione non sono modificate. Nel caso di raccomandazioni “a condizione”, in cui le condizioni per preferire un'opzione siano di carattere contestuale (disponibilità di risorse, costo efficacia, impatto organizzativo) il gruppo di lavoro può declinare quali siano le attuali condizioni del contesto italiano; modifiche sostanziali nel contesto potrebbero portare ad un adattamento della raccomandazione (v. punto successivo)
- **adattamento:** sono modificate la direzione e/o la forza della raccomandazione.

Il CTS ritiene che le raccomandazioni che sono sia coerenti con la legislazione italiana sia con le pratiche correnti, per cui quindi è improbabile che ci siano discrepanze nei giudizi di fattibilità e accettabilità, abbiano come esito finale l'adozione. Per questo motivo, il CTS sottopone al Panel i

diversi PICO accompagnati da una valutazione preliminare degli stessi secondo i criteri di coerenza sopra citati e dando una delle due possibili indicazioni: adozione oppure adattamento.

#### *Ruolo e funzioni del PICO Responsible Unit (PRU)*

Il PICO responsible unit (unità responsabile di un PICO – PRU) è gruppo di panelisti che include un metodologo panelista, un membro laico del panel e altri 2/3 panelisti con profilo clinico inerente ai PICO in oggetto o che abbiamo partecipato allo sviluppo dei PICO delle Linee Guida Europee. Possono inoltre partecipare anche i chair o vice chair. I membri di un PRU possono essere candidati dal gruppo di coordinamento o candidarsi spontaneamente.

L'attività del PRU si concretizza nella compilazione dell'EtD per la raccomandazione italiana (finestra “adoption” in GRADEPro inclusi i giudizi sui criteri) che viene inviato al panel per il pre-voto (almeno due settimane prima della plenaria) e nella presentazione del rationale e sintesi delle valutazioni durante la plenaria stessa.

#### *Metodi per giungere alla formulazione della nuova raccomandazione: adattamento*

In questo caso, il CTS sottopone al Panel uno o più PICO con l'indicazione di ripercorrere l'EtD in funzione di un adattamento al contesto italiano.

1. I membri del PRU prendono visione degli EtD delle raccomandazioni europee riportate nel sito ECIBC e interagiscono in teleconferenza con i panelisti che hanno partecipato alla loro stesura, che possono essere essi stessi membri del PRU o meno

1) Uno o più membri del PRU effettuano una ricognizione preliminare delle evidenze supplementari e le presentano durante una seconda teleconferenza del PRU, durante la quale il gruppo le valuta e si esprime seguendo la flow chart 1 per le evidenze recenti relative a desirable e undesirable effects e la flow chart 2 per le evidenze sugli elementi di contesto (costi, costo-efficacia, accettabilità, fattibilità, valori e preferenze)

2) Sulla base delle decisioni prese nel passaggio numero 2 il PRU procede alla stesura dell'EtD italiano per il pre-voto italiano e formula un nuovo giudizio sui criteri per i PICO che non hanno richiesto un passaggio con il CTS secondo quanto previsto nelle flow-chart. Questa fase può svolgersi interamente da remoto se non sussistono temi particolari che richiedano un ulteriore confronto del PRU in teleconferenza.

3) Il PRU invia al panel almeno due settimane prima del meeting virtuale la bozza dell'EtD per l'effettuazione di un pre-voto del giudizio sui criteri tramite la funzione Panel Voice del software GradePro.

- 4) Un membro del PRU introduce rationale e sintesi delle valutazioni all'inizio del meeting del panel
- 5) Il panel, guidato dai chairs, procede nella formulazione della raccomandazione secondo le procedure standard indicate dal metodo GRADE (3).

Come riportato nelle flow-chart riportate in coda al documento, due casi richiedono un confronto con il CTS prima della prosecuzione della stesura dell'EtD italiano:

- Evidenze su desirable e undesirable effects provenienti da studi recenti che possono modificare in modo significativo il giudizio del panel italiano: in questo caso, il CTS valuterà se richiedere una revisione sistematica completa di aggiornamento e valutazione delle evidenze, raccordandosi in questo senso con l'aggiornamento della raccomandazione europea organizzato dal JRC.
- Evidenze di contesto che possono modificare in modo significativo una raccomandazione in adozione: in questo caso, il CTS valuta la mozione del PRU rispetto alla propria valutazione di adozione e può modificare o meno il mandato al PRU verso l'adattamento.

Questi casi possono richiedere un posticipo della discussione del PICO in oggetto rispetto a quanto calendarizzato.

Il PRU può inoltre proporre al panel una riformulazione del PICO qualora non venga più considerato utile o pertinente alle necessità di decisioni cliniche. La riformulazione del PICO obbliga a una nuova revisione sistematica e dunque deve essere sottoposta al processo di prioritizzazione. Un PICO può essere riformulato quando, ad esempio, cambia leggermente la popolazione (es. una raccomandazione fatta per le sole micro-calcificazioni può essere estesa a micro e micro più lesione o viceversa), oppure l'intervento o il comparatore sono leggermente ridefiniti (es. tomo con o senza 2D sintetica può diventare tomo con 2D sintetica) perché la letteratura ha portato a definire il background del PICO in modo leggermente differente.

#### *Metodi per giungere alla formulazione della nuova raccomandazione: adozione*

In questo caso, il CTS sottopone al Panel uno o più PICO con l'indicazione di adottare la raccomandazione delle *Linee Guida Europee*.

1. Si costituisce un PRU che può essere di numerosità inferiore a quello previsto per le raccomandazioni in adattamento
  - 1) Il PRU acquisisce il materiale caricato su GRADEPro durante il processo di sviluppo delle *Linee Guida Europee* e prepara una bozza dell'EtD in italiano



2) Il PRU invia al panel almeno due settimane prima del meeting virtuale la bozza dell'EtD. I giudizi sui criteri non sono modificati e la funzione di pre-voto (“d’accordo” /” non d’accordo”) riguarda esclusivamente la raccomandazione finale. Se almeno l’80% del panel vota “d’accordo” la raccomandazione è approvata senza necessità di discussione in plenaria.

Durante questa fase di pre-analisi delle raccomandazioni, i membri del panel possono segnalare la necessità di adattare la raccomandazione e la richiesta viene trasmessa al CTS. Se il CTS accetta la mozione, la discussione del PICO viene rimandata ad una seduta successiva e viene nominato un PRU completo.

### **3.5 Formato previsto delle linee guida finali**

Le linee guida saranno disponibili attraverso la pagina di consultazione delle linee guida di SNLG e sul sito dell'Osservatorio Nazionale Screening. Inoltre, le società scientifiche facenti parte del CTS dovranno segnalarle sui loro siti.

### **3.6 Modalità di comunicazione ad interim e finale**

Una volta completato un gruppo di raccomandazioni che costituisca un corpus sensato e di senso compiuto di raccomandazioni, questo viene inviato a SNLG per la valutazione e l’approvazione. I metodi e i risultati delle raccomandazioni saranno anche resi disponibili sotto forma di pubblicazione scientifica nazionale o internazionale.

### **3.7 Prospettive per lo sviluppo di un “percorso donna”**

Un limite dell’approccio delle linee guida “per PICO” è la frammentarietà delle raccomandazioni, che appaiono come indicazioni scollegate e non permettono di delineare un percorso che la donna e i professionisti possano seguire. Il CTS ha discusso della possibilità ampliare l’ambito di attività del panel al di là dell’adoption dell’ECIBC fino ad arrivare alla proposta di un PDTA nazionale per la prevenzione e la diagnosi del tumore della mammella nelle donne a medio rischio. L’obiettivo sarebbe fornire alla donna e ai portatori di interesse raccomandazioni basate sulla migliore evidenza disponibile, su quali interventi diagnostici o di prevenzione possono essere adottati con l’obiettivo di prevenire o diagnosticare precocemente il tumore della mammella in base alla propria fascia di età. Questa progettualità è stata ritenuta di interesse e sarà ridiscussa ed eventualmente oggetto di un aggiornamento di questo documento metodologico al termine del percorso di adoption delle Linee Guida Europee.

#### **4. Revisione esterna:**

Il documento che includeva gli EtD approvati e revisionati dal Panel è stato inviato ad esperti esterni per una revisione del contenuto e dell'interpretazione delle prove a supporto delle raccomandazioni. Sono stati identificati tre revisori le cui competenze coprivano gli ambiti principali di interesse delle raccomandazioni sottoposte a revisione: un revisore con profilo diagnostico-clinico (radiologo) e due anatomopatologi. I membri del panel estensori della versione finale degli EtD hanno prodotto un riscontro punto per punto delle osservazioni dei revisori, che hanno dato luogo a modifiche del testo quando ritenute opportune dal Panel. Tutti gli esperti hanno dichiarato il loro conflitto di interessi.

#### **5. Applicabilità**

Le raccomandazioni di questa LG sono state elaborate e formulate per rendere direttamente applicabili alla popolazione italiana le evidenze scientifiche sulla diagnosi precoce del cancro della mammella. Il Panel segnala la presenza di fattori potenzialmente ostacolanti quali la persistenza di percorsi di tipo opportunistico e spontaneo per sottoutilizzo dei percorsi organizzati per scarsa conoscenza o problematiche organizzative. Questa LG si propone come primo documento condiviso da tutte le società scientifiche coinvolte nel percorso verso una maggiore standardizzazione e appropriatezza del percorso di diagnosi precoce in Italia.

#### **6. Aggiornamento della LG: tempi e modalità**

In considerazione della continua evoluzione delle conoscenze medico scientifiche e della conseguente disponibilità della letteratura d'interesse, l'aggiornamento del documento è previsto in concordanza con l'aggiornamento delle linee guida europee, descritto nel documento ECIBC Guidelines updating strategy workflow (<https://healthcare-quality.jrc.ec.europa.eu/ecibc/methodologies/guidelines-updating>)

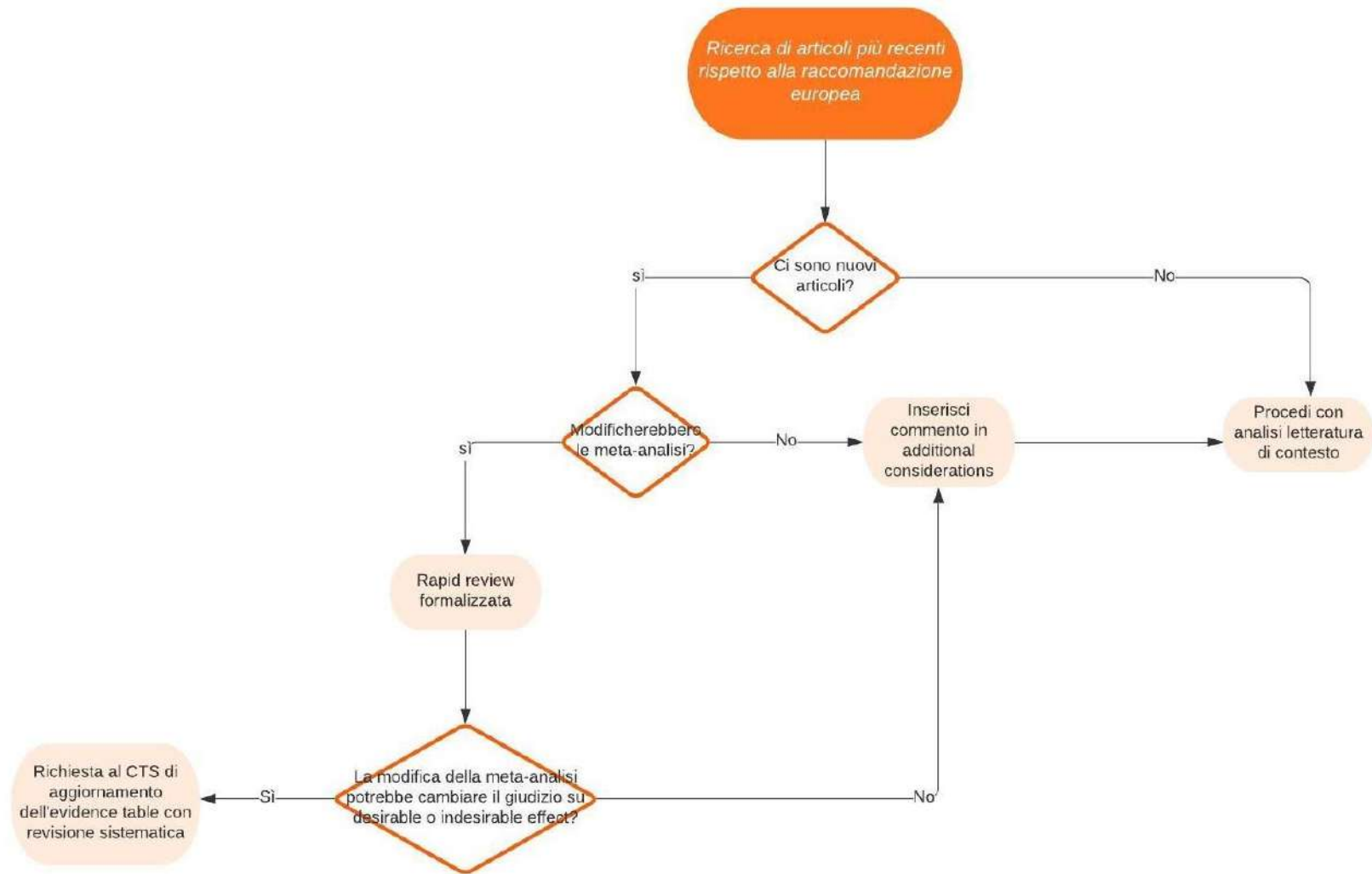
#### **7. Conflitti di interesse editoriale**

I membri del panel hanno sottoscritto una dichiarazione su eventuali conflitti di interesse. I membri del panel si astengono dalla votazione della forza della raccomandazione nei seguenti casi:

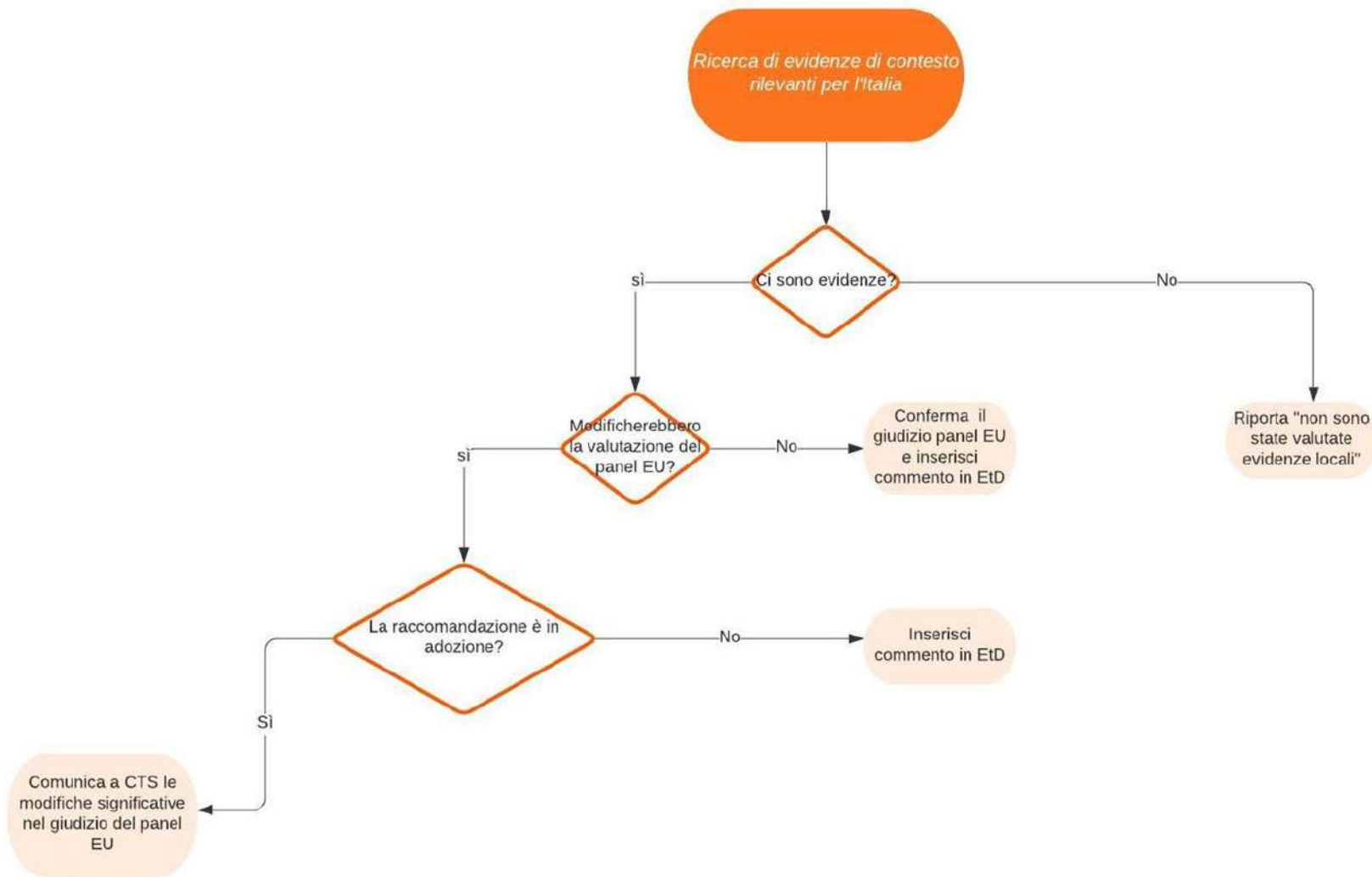
- Quando fanno parte dell'*authorship* di uno o più lavori considerati per la raccomandazione.
- Quando hanno ricevuto finanziamenti diretti o indiretti da aziende titolari dell'intervento che si sta prendendo in esame.

## BIBLIOGRAFIA

- 1) N. Perry, M. Broeders, C. de Wolf, S. Törnberg, R. Holland, L. von Karsa, 2006. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth Edition. European Breast Cancer Network (EBCN), Lyon.
- 2) European Commission Initiative on Breast Cancer. Recommendations for the European Breast Cancer Guidelines, <https://ecibc.jrc.ec.europa.eu/recommendations>; 2019
- 3) Alonso-Coello P et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016 a;353: i2016; doi: <https://doi.org/10.1136/bmj.i2016a>
- 4) Schünemann HJ et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADEADOLPMENT. J Clin Epidemiol. 2017 Jan; 81:101-110. doi: 10.1016/j.jclinepi.2016.09.009. Epub 2016 Oct.
- 5) Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure. Manuale metodologico per la produzione di linee guida di pratica clinica. [https://snlg.iss.it/wp-content/uploads/2019/04/MM\\_v1.3.2\\_apr\\_2019.pdf](https://snlg.iss.it/wp-content/uploads/2019/04/MM_v1.3.2_apr_2019.pdf)



Flow-chart 1: Desirable e undesirable effects



Flow-chart 2: Elementi di contesto

## **REGOLE PER IL PANEL**

### **1. Chair e vice-chair**

Chair e vice-chair clinici: Marco Rosselli del Turco e Francesca Pietriabiasi

Chair e vice-chair metodologici: Silvia Deandrea e Matteo Capobussi

Chair e vice-chair epidemiologici: Lauro Bucchi e Carlo Senore

Il panel prevede tre tipologie di chair: clinico, epidemiologico e metodologico. I tre soggetti individuati rappresentano competenze, rispettivamente, in ambito diagnostico del cancro della mammella, in ambito screenologico e in metodologia di sviluppo delle linee guida con GRADE. Per ogni profilo è anche identificato un vice-chair.

I chair e vice chair sono scelti tra i membri del panel da parte del CTS su proposta del gruppo di coordinamento e indirizzo e sono eletti nel corso della prima riunione del panel.

Ciascuna plenaria del panel è condotta da uno dei chair, a seconda dell'ordine del giorno. In caso di assenza del chair, il meeting è condotto dal vice-chair.

### **2. Modalità di sostituzione dei chair e dei membri del panel dimissionari**

In caso di dimissioni di un chair o di un vice chair, si ripete la procedura di elezione dettagliata al punto 1 per identificare un sostituto.

### **3. Membri associati/supplementari**

Il CTS può individuare delle figure professionali non rappresentate all'interno del panel (ad esempio economista, antropologo, etc.) per ottenere contributi su tematiche specifiche. A queste professionalità saranno applicate le procedure relative al conflitto di interesse.

### **4. Osservatori**

Non è prevista la partecipazione di osservatori.

### **5. PICO Responsible Unit - PRU**

Il panel può avviare lavori attraverso PRU dedicato ad un singolo PICO o a un gruppo di PICO collegati fra loro. I PRU devono vedere integrate le varie funzioni e competenze, in particolare devono prevedere la partecipazione di chi ha condotto le revisioni e le eventuali integrazioni alla letteratura e gli esperti del panel. In ogni PRU, ci sarà un rapporteur che si farà carico della presentazione delle conclusioni della PRU in plenaria e che, nel caso non siano presenti all'interno della PRU, si rapporterà con i chair ed i vice-chair.

### **6. Agenda dei meeting**

L'ordine del giorno dei meeting del panel è proposto dall'Osservatorio Nazionale Screening, in accordo con le indicazioni dello Steering Committee.

## **7. Convocazione dei meeting**

La convocazione dei meeting è a cura della segreteria ONS. In considerazione anche della particolare situazione sanitaria, saranno inizialmente programmate sessioni in videoconferenza che potranno essere successivamente affiancate o sostituite, se le condizioni lo permettono, da riunioni in presenza.

## **8. Preparazione dei meeting**

La prima seduta del panel prevede la candidatura e nomina dei chair. Segue quindi una sessione di formazione e a seguire la votazione del primo PICO. A partire dalla seduta successiva, per ogni sessione di plenaria (che può avere in agenda uno o più PICO) la segreteria ONS richiede ai panelisti di indicare l'interesse per la tematica in discussione e di garantire la presenza alla plenaria con effettuazione del pre-voto tramite la funzione Panel Voice del software GradePro nei tempi richiesti. Il CTS insieme al gruppo di coordinamento valuta se il numero di panelisti che hanno dato conferma di adesione per la data può plausibilmente permettere di includere tutte le professionalità ritenute indispensabili dalla specifica tematica dei PICO e una pluralità di prospettive. Se le condizioni non sono verificate si procede a una cooptazione attiva di ulteriori membri del panel.

## **9. Regole di deliberazione del panel**

Il panel effettua l'attività propria di formulazione delle raccomandazioni in accordo alle regole del metodo GRADE-Evidence to Decision, delineate nelle pubblicazioni corrispondenti. Per la direzione della raccomandazione e per il giudizio sui criteri dell'EtD è sufficiente la maggioranza semplice, mentre per la forza della raccomandazione è necessaria una maggioranza qualificata (80%).

Perché la votazione sia valida è necessario che sia presente il 50%+1 dei panelisti che hanno dato l'adesione per il PICO in discussione, sia per le votazioni in plenaria sia per le votazioni in pre-voto con il software.

Il Panel è tenuto a deliberare su tutte le raccomandazioni, sia quelle in adattamento che quelle in adozione. La deliberazione sulla raccomandazione in adozione avviene esclusivamente attraverso la funzione di voto del software GRADEPro, tranne nel caso di raccomandazione finale per cui ha espresso disaccordo almeno il 20% dei panelisti. In questo caso, si ritiene il voto elettronico non valido e si procede a votazione in plenaria.

## **10. Verbali delle sedute**

I contenuti sono rappresentati dai risultati dell'EtD, con l'aggiunta di eventuali altre decisioni extra EdT. Il verbale è redatto dalla segreteria ONS.

## 11. Protezione dati personali

I dati personali dei membri del panel sono conservati a cura della segreteria ONS in modalità sicura.

## 12. Gestione del conflitto di interesse

Il CTS valuta i moduli di conflitto compilati dai tutti i componenti del panel e assegna, seguendo i principi definiti dal Guidelines International Network (Schunemann et al, 2015) ad ogni dichiarazione uno di tre livelli di potenziale conflitto:

1. minimo o insignificante

2. potenzialmente rilevante

3. rilevante

Il CTS ha effettuato l'analisi dei COI e non ha rilevato alcun conflitto di interesse rilevante.

La valutazione del conflitto di interesse è specifica per gruppi di PICO collegati fra loro. Si userà il modulo proposto dal Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure dell'Istituto Superiore di Sanità (appendice 5 del Manuale metodologico per la produzione di linee guida di pratica clinica [https://snlg.iss.it/wp-content/uploads/2019/04/MM\\_v1.3.2\\_apr\\_2019.pdf](https://snlg.iss.it/wp-content/uploads/2019/04/MM_v1.3.2_apr_2019.pdf)).

Si richiede al panel di mantenere la confidenzialità sui contenuti delle sedute fino al momento della release della raccomandazione. Saranno comunque messi a disposizione sul sito ONS i documenti principali, il cronoprogramma e un aggiornamento puntuale su quali PICO sono stati già trattati.

## Riferimenti

GRADE Guidelines series: <https://www.jclinepi.com/content/jce-GRADE-Series> Schünemann HJ, Al-Ansary LA, Forland F, et al. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. Ann Intern Med. 2015;163(7):548-553. doi:10.7326/M14-1885.



## ETD

### QUESITO 1

#### Dovrebbe risonanza magnetica aggiuntiva vs nessuna risonanza magnetica aggiuntiva essere utilizzato per donne con conferma istologica di carcinoma duttale in situ per il planning preoperatorio

POPULATION:	donne con carcinoma duttale in situ istologicamente confermato (DCIS)
INTERVENTION:	risonanza magnetica aggiuntiva
COMPARISON:	nessuna risonanza magnetica aggiuntiva
MAIN OUTCOMES:	Modifica del trattamento causata dalla MRI (da conservativo a mastectomia o da mastectomia unilaterale a bilaterale); chirurgia conservativa della mammella iniziale; proporzione di reinterventi dopo chirurgia conservativa (re-escissione o conversione a mastectomia); proporzione di margini positivi dopo chirurgia conservativa; mastectomia; disease-free survival (inferito da ricorrenza loco-regionale); qualità della vita; eventi avversi diretti
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	<p>Il carcinoma duttale in situ (DCIS) è la forma più comune di cancro non invasivo. Il DCIS rappresenta un gruppo eterogeneo di cellule maligne confinate entro la membrana basale dell'epitelio duttale (1). Negli ultimi anni la diagnosi di DCIS si è accresciuta, per lo più attribuibile all'ampia diffusione della mammografia di screening, tanto che questo tipo di lesioni rappresentano al giorno d'oggi dal 20 al 25 percento delle nuove diagnosi di cancro della mammella (2)</p> <p>In teoria, l'uso di MRI aggiuntiva dopo la mammografia standard può migliorare la definizione dell'estensione del DCIS nel momento del planning pre-operatorio e potenzialmente ridurre la necessità di chirurgia aggiuntiva dopo la conservativa, specie nel contesto di microcalcificazioni estese. Tuttavia, il ruolo della MRI nella gestione del DCIS rimane da chiarire, mentre alcuni studi mostrano una altra sensibilità a confronto con la mammografia altri studi suggeriscono che la risonanza non abbia vantaggi nel controllo locale del DCIS o addirittura può sovrastimare la diffusione della lesione portando a un numero aumentato e non necessario di biopsie chirurgiche (3)(4) o mastectomie.</p>
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

### VALUTAZIONE

Problem		
Is the problem a priority?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	

<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Ductal carcinoma in situ (DCIS) is the most common form of non-invasive breast cancer. DCIS of the breast represents a heterogeneous group of malignant cells confined within the basement membrane of the ductal epithelium (1). In the last years detection of DCIS has increased, mostly attributed to the widespread use of screening mammography, as this type of lesions accounts nowadays for 20 to 25 percent of new breast cancer diagnosis (2). Thus, whether the use of preoperative MRI in these patients translates to clinical advantages or to a positive balance between benefits and harms remains unclear.</p>	The GDG prioritized this question for the ECIBC.
Adolopment		
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Il panel ritiene che sia una pratica consolidata. Lo confermano i dati derivati dalla casistica dei casi piemontesi raccolti da SQTm negli anni 2010-2020. Da questa raccolta emerge un graduale aumento dell'utilizzo preoperatorio della MRI che passa dal 17% (2010) al 43% (2020). Rimane mediamente del 15% il numero dei casi per cui questa informazione è mancante.

## Desirable Effects

How substantial are the desirable anticipated effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE																																																
	Original																																																	
<ul style="list-style-type: none"> <li>● Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr style="background-color: #2e75b6; color: white;"> <th style="width: 15%;">Outcomes</th> <th style="width: 15%;">N<sup>o</sup> of participants (studies) Follow up</th> <th style="width: 15%;">Certainty of the evidence (GRADE)</th> <th style="width: 10%;">Relative effect (95% CI)</th> <th colspan="2" style="width: 45%;">Anticipated absolute effects* (95% CI)</th> </tr> <tr style="background-color: #d9d9d9;"> <th></th> <th></th> <th></th> <th></th> <th style="width: 15%;">Risk with no additional magnetic resonance imaging</th> <th style="width: 30%;">Risk difference with additional magnetic resonance imaging</th> </tr> </thead> <tbody> <tr> <td>Initial BCS - RCT</td> <td>80 (1 RCT)<sup>1</sup></td> <td>⊕○○○ VERY LOW<sup>a,b,c</sup></td> <td><b>RR 1.05</b> (0.77 to 1.42)</td> <td colspan="2">Study population</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td>659 per 1000</td> <td><b>33 more per 1000</b> (151 fewer to 277 more)</td> </tr> <tr> <td>Initial BCS - Cohorts</td> <td>3991 (7 observational studies)<sup>2,3,4,5,6,7,8</sup></td> <td>⊕○○○ VERY LOW<sup>d,e,f</sup></td> <td><b>OR 0.45</b> (0.27 to 0.76)</td> <td colspan="2">Study population</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td>759 per 1000</td> <td><b>173 fewer per 1000</b> (299 fewer to 54 fewer)</td> </tr> <tr> <td>Proportion of positive margins after BCS - RCT</td> <td>91 (1 RCT)<sup>9</sup></td> <td>⊕○○○ VERY LOW<sup>b,c,g</sup></td> <td><b>RR 1.58</b> (0.85 to 2.92)</td> <td colspan="2">Study population</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td>250 per 1000</td> <td><b>145 more per 1000</b> (38 fewer to 480 more)</td> </tr> </tbody> </table>	Outcomes	N <sup>o</sup> of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)						Risk with no additional magnetic resonance imaging	Risk difference with additional magnetic resonance imaging	Initial BCS - RCT	80 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,c</sup>	<b>RR 1.05</b> (0.77 to 1.42)	Study population						659 per 1000	<b>33 more per 1000</b> (151 fewer to 277 more)	Initial BCS - Cohorts	3991 (7 observational studies) <sup>2,3,4,5,6,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.45</b> (0.27 to 0.76)	Study population						759 per 1000	<b>173 fewer per 1000</b> (299 fewer to 54 fewer)	Proportion of positive margins after BCS - RCT	91 (1 RCT) <sup>9</sup>	⊕○○○ VERY LOW <sup>b,c,g</sup>	<b>RR 1.58</b> (0.85 to 2.92)	Study population						250 per 1000	<b>145 more per 1000</b> (38 fewer to 480 more)	<p>The GDG agreed that the desirable outcomes are: MRI triggered treatment change (from breast conservative to mastectomy or from unilateral to bilateral mastectomy rate); Initial breast conservative surgery (BCS); Disease-free survival (inferred from loco-regional recurrence); Quality of life.</p> <p>The GDG judged that the desirable effects are trivial.</p> <p>The results of the surgical and clinical outcomes were complemented with data on accuracy (detection of lesions, size correlation, or under/oversize estimation) reported in the same included studies.</p> <p>We did not found studies reporting in QoL. But a judgement about this outcome might be inferred from initial BCS, total mastectomy and loco-regional recurrence estimates.</p>
Outcomes	N <sup>o</sup> of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)																																														
				Risk with no additional magnetic resonance imaging	Risk difference with additional magnetic resonance imaging																																													
Initial BCS - RCT	80 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,c</sup>	<b>RR 1.05</b> (0.77 to 1.42)	Study population																																														
				659 per 1000	<b>33 more per 1000</b> (151 fewer to 277 more)																																													
Initial BCS - Cohorts	3991 (7 observational studies) <sup>2,3,4,5,6,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.45</b> (0.27 to 0.76)	Study population																																														
				759 per 1000	<b>173 fewer per 1000</b> (299 fewer to 54 fewer)																																													
Proportion of positive margins after BCS - RCT	91 (1 RCT) <sup>9</sup>	⊕○○○ VERY LOW <sup>b,c,g</sup>	<b>RR 1.58</b> (0.85 to 2.92)	Study population																																														
				250 per 1000	<b>145 more per 1000</b> (38 fewer to 480 more)																																													

Proportion of positive margins after BCS - Cohorts	3212 (6 observational studies) <sup>10,11,2,5,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.95</b> (0.67 to 1.35)	Study population		
				185 per 1000	<b>8 fewer per 1000</b> (53 fewer to 50 more)	
	Proportion of re-operation after BCS (Re-operation rate) - RCT	55 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>b,c</sup>	<b>RR 1.44</b> (0.79 to 2.64)	Study population	
					370 per 1000	<b>163 more per 1000</b> (78 fewer to 607 more)
	Proportion of re-operation after BCS (Re-operation rate) - Cohorts	1654 (10 observational studies) <sup>11,12,2,3,6,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.97</b> (0.63 to 1.48)	Study population	
					237 per 1000	<b>5 fewer per 1000</b> (73 fewer to 78 more)
	Mastectomy (total mastectomy rate) - RCT	80 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>b,c</sup>	<b>RR 0.79</b> (0.48 to 1.31)	Study population	
					488 per 1000	<b>102 fewer per 1000</b> (254 fewer to 151 more)
Mastectomy (total mastectomy rate) - Cohorts	1283 (4 observational studies) <sup>11,2,3,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 1.59</b> (0.90 to 2.81)	Study population		
				235 per 1000	<b>93 more per 1000</b> (18 fewer to 228 more)	
Disease free survival (inferred from locoregional recurrence) - Cohorts	2347 (2 observational studies) <sup>10,13</sup>	⊕○○○ VERY LOW <sup>h,i,j</sup>	<b>OR 1.17</b> (0.79 to 1.73)	Study population		
				82 per 1000	<b>13 more per 1000</b> (16 fewer to 52 more)	
MRI triggered treatment change - Cohort	750 (6 observational studies) <sup>14,15,16,17,18,3</sup>	⊕⊕○○ LOW	-	The pooled proportion of treatment change was 19% (95% CI 13% to 24%; I2 67%). (n/N= 127/750).		
Quality of Life - not reported	-	-	-	-	-	
Direct adverse events - not reported	-	-	-	-	-	
<ol style="list-style-type: none"> <li>Peters NH, van Esser S, van den Bosch MA, Storm RK, Plaisier PW, van Dalen T, Diepstraten SC, Weits T, Westenend PJ, Stapper G, Fernandez-Gallardo MA, Borel Rinkes IH, van Hillegerberg R, Mali WP, Peeters PH.. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. Eur J Cancer; 2011.</li> <li>Vos, E. L., Voogd, A. C., Verhoef, C., Siesling, S., Obdeijn, I. M., Koppert, L. B.. Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry. Br J Surg; Dec 2015.</li> </ol>						

The included randomized clinical trials (RCT) were not designed to assess the clinical question of interest. The extracted data come from subgroups of the reported results and thus are highly imprecise and subject to selection bias.

The body evidence includes results from observational studies (cohorts) given the limitations of the identified RCTs.

The certainty of evidence was very low, there was no data to support a potential benefit from the intervention.

3. Pilewskie M, Kennedy C, Shappell C, Helenowski I, Scholtens D, Hansen N, Bethke K, Jeruss J., Karstaedt, P., Khan, S. A.. Effect of MRI on the management of ductal carcinoma in situ of the breast. *Ann Surg Oncol*; 2013.
4. Onega T, Weiss JE, Goodrich ME, Zhu W, DeMartini WB, Kerlikowske K, Ozanne E, Tosteson A. N. A., Henderson, L. M., Buist, D. S. M., Wernli, K. J., Herschorn, S. D., Hotaling, E., O'Donoghue, C., Hubbard, R.. Relationship between preoperative breast MRI and surgical treatment of non-metastatic breast cancer. *J Surg Oncol*; 2017.
5. Itakura K, Lessing J, Sakata T, Heinzerling A, Vriens E, Wisner D, Alvarado M, Esserman L, Ewing C, Hylton N, Hwang ES.. The impact of preoperative magnetic resonance imaging on surgical treatment and outcomes for ductal carcinoma in situ. *Clin Breast Cancer*; 2011.
6. Hajaj, M., Karim, A., Pascaline, S., Noor, L., Patel, S., Dakka, M.. Impact of MRI on high grade Ductal Carcinoma In situ (HG DCIS) management, are we using the full scope of MRI?. *Eur J Radiol*; Oct 2017.
7. Davis, K. L., Barth, R. J., Jr., Gui, J., Dann, E., Eisenberg, B., Rosenkranz, K.. Use of MRI in preoperative planning for women with newly diagnosed DCIS: risk or benefit?. *Ann Surg Oncol*; Oct 2012.
8. Allen, L. R., Lago-Toro, C. E., Hughes, J. H., Careaga, E., Brown, A. T., Chernick, M., Barrio, A. V., Frazier, T. G.. Is there a role for MRI in the preoperative assessment of patients with DCIS?. *Ann Surg Oncol*; Sep 2010.
9. Turnbull, L. W., Brown, S. R., Olivier, C., Harvey, I., Brown, J., Drew, P., Hanby, A., Manca, A., Napp, V., Sculpher, M., Walker, L. G., Walker, S.. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). *Health Technol Assess*; Jan 2010.
10. Pilewskie, M., Olcese, C., Eaton, A., Patil, S., Morris, E., Morrow, M., Van Zee, K. J.. Perioperative breast MRI is not associated with lower locoregional recurrence rates in DCIS patients treated with or without radiation. *Ann Surg Oncol*; May 2014.
11. Kropcho, L. C., Steen, S. T., Chung, A. P., Sim, M. S., Kirsch, D. L., Giuliano, A. E. Preoperative breast MRI in the surgical treatment of ductal carcinoma in situ. *Breast J*; Mar-Apr 2012.
12. So, A., De La Cruz, L. M., Williams, A. D., Bahng, J., Liao, G., McDonald, E. S., Fisher, C. S., Czerniecki, B. J., Sataloff, D., Tchou, J. The impact of preoperative magnetic resonance imaging and lumpectomy cavity shavings on re-excision rate in pure ductal carcinoma in situ-A single institution's experience. *J Surg Oncol*; Mar 2018.
13. Vapiwala N, Hwang WT, Kushner CJ, Schnall MD, Freedman GM, Solin LJ.. No impact of breast magnetic resonance imaging on 15-year outcomes in patients with ductal carcinoma in situ or early-stage invasive breast cancer managed with breast conservation therapy. *Cancer*; 2017.
14. Pettit, K., Swatske, M. E., Gao, F., Salavaggione, L., Gillanders, W. E., Aft, R. L., Monsees, B. S., Eberlein, T. J., Margenthaler, J. A. The impact of breast MRI on surgical decision-making: are patients at risk for mastectomy?. *J Surg Oncol*; Dec 1 2009.
15. Obdeijn IM, Tilanus-Linthorst MM, Spronk S, van Deurzen CH, de Monye C, Hunink MG, Menke MB.. Preoperative breast MRI can reduce the rate of tumor-positive resection margins and reoperations in patients undergoing breast-conserving surgery. *AJR Am J Roentgenol*; 2013.
16. Lee, J., Jung, J. H., Kim, W. W., Hwang, S. O., Kim, H. J., Park, J. Y., Chae, Y. S., Yang, J. D., Park, H. Y. The role of preoperative breast magnetic resonance (MR) imaging for surgical decision in patients with triple-negative breast cancer. *J Surg Oncol*; Jan 2016.
17. Hlubocky, J., Bhavnagri, S., Swinford, A., Mitri, C., Rebner, M., Pai, V.. Does the use of pre-treatment MRI change the management of patients with newly diagnosed breast cancer? *Breast J*; Nov 5 2017.

	<p>18. Duygulu G, Oktay A, Bilgen IG, Kapkaç M, Zekioğlu O.. The role of breast MRI in planning the surgical treatment of breast cancer. <i>Diagn Interv Radiol</i>; 2012.</p> <ul style="list-style-type: none"> <li>a. Downgraded due that initial BCS is not an end outcome, as later women might have received re-excision or a mastectomy depending on the status of operative margins.</li> <li>b. The number of events from the patients recruited in each arm is much lower than the minimum required to have adequate power.</li> <li>c. The intervention (preoperative MRI) was not feasible to be blinded which originated a performance high risk of bias which might have impacted on the surgeon initial planning decision.</li> <li>d. In some cohort studies, the comparison was between arms over different periods of time (no overlapping), and thus potentially introducing a high risk of secular bias.</li> <li>e. The majority of studies reported measurement of association as crude estimates or it had to be calculated from crude numbers.</li> <li>f. There is a high heterogeneity in the estimated effect across the included studies ranging from significant benefit to harm.</li> <li>g. The definition of positive margins was variable across the different clinical centres included (distance from operative margins) this might have introduced a misclassification bias.</li> <li>h. Downgraded due to be a surrogate outcome of disease-free survival.</li> <li>i. A proportion of patients had breast MRI performed after lumpectomy or at re-excision stage which does not directly apply to the clinical pathway of interest.</li> </ul>	
--	--	--

19. The confidence interval of the effect size ranged from significant benefit to harm.

Study Id	N patients	Diagnostic outcomes	Clinical outcomes
Pilewskie 2012*	352	Multifocal abnormality seen: MM: 15.3%; MRI: 32.6%	
		Bilateral abnormality seen: MM: 6.5%; MRI: 25.7%	Initial BCS: OR 0.71 (0.45 to 1.14).
		Accurate size estimation: MM: 52.1%; MRI: 41.1%	Re-excision rate: OR 0.67 (0.38 to 1.18).
		Size underestimation by 1 cm or more: MM: 13.2%; MRI: 15%	Total mastectomy rate: OR 1.52 (0.95 to 2.41)
		Size overestimated by 1 cm or more: MM: 34.7%; MRI: 43.9%	Treatment change: 15% (11% to 21%)
Hajaj 2017*	122	MRI showed a better histological size correlation compared to MM.	Initial BCS: OR 0.04 (0.01 to 0.17). Re-excision rate: OR 0.55 (0.19 to 1.62).
Davis 2012	218	Identification of additional lesions: 26/154 (16.9%; 10 were biopsy-confirmed and 8 lead to wider lumpectomy).  Detection of invasive contralateral lesions: 4.5% (2 invasive, 5 DCIS)	Initial BCS: OR 0.88 (0.42 to 1.84). Re-excision rate: OR 0.92 (0.48 to 1.78). Total mastectomy rate: OR 1.27 (0.64 to 2.49)

\*the comparison was not made over the same samples as the MRI arm is made of about 60% of the subjects included in the mammography arm.

Adolopment

- Trivial
- Small
- Moderate
- Large
- Varies
- Don't know

Non sono state considerate evidenze di contesto per l'Italia

.

**Undesirable Effects**

How substantial are the undesirable anticipated effects?

**GIUDIZI**

**RICERCA DELLE PROVE DI EVIDENZA**

**CONSIDERAZIONI AGGIUNTIVE**

Original

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no additional magnetic resonance imaging	Risk difference with additional magnetic resonance imaging
Initial BCS - RCT	80 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,c</sup>	<b>RR 1.05</b> (0.77 to 1.42)	Study population	
				659 per 1000	<b>33 more per 1000</b> (151 fewer to 277 more)
Initial BCS - Cohorts	3991 (7 observational studies) <sup>2,3,4,5,6,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.45</b> (0.27 to 0.76)	Study population	
				759 per 1000	<b>173 fewer per 1000</b> (299 fewer to 54 fewer)
Proportion of positive margins after BCS - RCT	91 (1 RCT) <sup>9</sup>	⊕○○○ VERY LOW <sup>b,c,g</sup>	<b>RR 1.58</b> (0.85 to 2.92)	Study population	
				250 per 1000	<b>145 more per 1000</b> (38 fewer to 480 more)
Proportion of positive margins after BCS - Cohorts	3212 (6 observational studies) <sup>10,11,2,5,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.95</b> (0.67 to 1.35)	Study population	
				185 per 1000	<b>8 fewer per 1000</b> (53 fewer to 50 more)
Proportion of re-operation after BCS (Re-operation rate) - RCT	55 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>b,c</sup>	<b>RR 1.44</b> (0.79 to 2.64)	Study population	
				370 per 1000	<b>163 more per 1000</b> (78 fewer to 607 more)
Proportion of re-operation after BCS (Re-operation rate) - Cohorts	1654 (10 observational studies) <sup>11,12,2,3,6,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 0.97</b> (0.63 to 1.48)	Study population	
				237 per 1000	<b>5 fewer per 1000</b> (73 fewer to 78 more)
Mastectomy (total mastectomy rate) - RCT	80 (1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>b,c</sup>	<b>RR 0.79</b> (0.48 to 1.31)	Study population	
				488 per 1000	<b>102 fewer per 1000</b> (254 fewer to 151 more)
				Study population	

The GDG agreed that the undesirable outcomes are: Proportion of re-operation after BCS (re-excision or conversion to mastectomy); Proportion of positive margins after BCS; Mastectomy; Direct adverse events.

The GDG judged that the undesirable effects are moderate.

A systematic review about the role of preoperative MRI versus no-MRI in all breast cancer histology suggested an unfavourable harm-benefit ratio for routine use of preoperative MRI in the management of breast cancer (MRI significantly increased mastectomy rates - adjusted OR, 1.51,  $P < 0.001$ -) (Houssami 2013).



Mastectomy (total mastectomy rate) - Cohorts	1283 (4 observational studies) <sup>11,2,3,7,8</sup>	⊕○○○ VERY LOW <sup>d,e,f</sup>	<b>OR 1.59</b> (0.90 to 2.81)	235 per 1000	<b>93 more per 1000</b> (18 fewer to 228 more)
Disease free survival (inferred from locoregional recurrence) - Cohorts	2347 (2 observational studies) <sup>10,13</sup>	⊕○○○ VERY LOW <sup>h,i,j</sup>	<b>OR 1.17</b> (0.79 to 1.73)	Study population	
				82 per 1000	<b>13 more per 1000</b> (16 fewer to 52 more)
MRI triggered treatment change - Cohort	750 (6 observational studies) <sup>14,15,16,17,18,3</sup>	⊕⊕○○ LOW	-	The pooled proportion of treatment change was 19% (95% CI 13% to 24%; I2 67%). (n/N= 127/750).	
Quality of Life - not reported	-	-	-	-	-
Direct adverse events - not reported	-	-	-	-	-

1. Peters NH, van Esser S, van den Bosch MA, Storm RK, Plaisier PW, van Dalen T, Diepstraten SC, Weits T, Westenend PJ, Stapper G, Fernandez-Gallardo MA, Borel Rinkes IH, van Hillegerberg R, Mali WP, Peeters PH.. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. *Eur J Cancer*; 2011.
2. Vos, E. L., Voogd, A. C., Verhoef, C., Siesling, S., Obdeijn, I. M., Koppert, L. B.. Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry. *Br J Surg*; Dec 2015.
3. Pilewskie M, Kennedy C, Shappell C, Helenowski I, Scholtens D, Hansen N, Bethke K, Jeruss J., Karstaedt, P., Khan, S. A.. Effect of MRI on the management of ductal carcinoma in situ of the breast. *Ann Surg Oncol*; 2013.
4. Onega T, Weiss JE, Goodrich ME, Zhu W, DeMartini WB, Kerlikowske K, Ozanne E, Tosteson A. N. A., Henderson, L. M., Buist, D. S. M., Wernli, K. J., Herschorn, S. D., Hotaling, E., O'Donoghue, C., Hubbard, R.. Relationship between preoperative breast MRI and surgical treatment of non-metastatic breast cancer. *J Surg Oncol*; 2017.
5. Itakura K, Lessing J, Sakata T, Heinzerling A, Vriens E, Wisner D, Alvarado M, Esserman L, Ewing C, Hylton N, Hwang ES.. The impact of preoperative magnetic resonance imaging on surgical treatment and outcomes for ductal carcinoma in situ. *Clin Breast Cancer*; 2011.
6. Hajaj, M., Karim, A., Pascaline, S., Noor, L., Patel, S., Dakka, M.. Impact of MRI on high grade Ductal Carcinoma Insitu (HG DCIS) management, are we using the full scope of MRI?. *Eur J Radiol*; Oct 2017.
7. Davis, K. L., Barth, R. J., Jr., Gui, J., Dann, E., Eisenberg, B., Rosenkranz, K.. Use of MRI in preoperative planning for women with newly diagnosed DCIS: risk or benefit?. *Ann Surg Oncol*; Oct 2012.
8. Allen, L. R., Lago-Toro, C. E., Hughes, J. H., Careaga, E., Brown, A. T., Chernick, M., Barrio, A. V., Frazier, T. G.. Is there a role for MRI in the preoperative assessment of patients with DCIS?. *Ann Surg Oncol*; Sep 2010.
9. Turnbull, L. W., Brown, S. R., Olivier, C., Harvey, I., Brown, J., Drew, P., Hanby, A., Manca, A., Napp, V., Sculpher, M., Walker, L. G., Walker, S.. Multicentre randomised controlled trial

	<p>examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). <i>Health Technol Assess</i>; Jan 2010.</p> <ol style="list-style-type: none"> <li>10. Pilewskie, M., Olcese, C., Eaton, A., Patil, S., Morris, E., Morrow, M., Van Zee, K. J.. Perioperative breast MRI is not associated with lower locoregional recurrence rates in DCIS patients treated with or without radiation. <i>Ann Surg Oncol</i>; May 2014.</li> <li>11. Kropcho, L. C., Steen, S. T., Chung, A. P., Sim, M. S., Kirsch, D. L., Giuliano, A. E.. Preoperative breast MRI in the surgical treatment of ductal carcinoma in situ. <i>Breast J</i>; Mar-Apr 2012.</li> <li>12. So, A., De La Cruz, L. M., Williams, A. D., Bahng, J., Liao, G., McDonald, E. S., Fisher, C. S., Czerniecki, B. J., Sataloff, D., Tchou, J.. The impact of preoperative magnetic resonance imaging and lumpectomy cavity shavings on re-excision rate in pure ductal carcinoma in situ-A single institution's experience. <i>J Surg Oncol</i>; Mar 2018.</li> <li>13. Vapiwala N, Hwang WT, Kushner CJ, Schnall MD, Freedman GM, Solin LJ.. No impact of breast magnetic resonance imaging on 15-year outcomes in patients with ductal carcinoma in situ or early-stage invasive breast cancer managed with breast conservation therapy. <i>Cancer</i>; 2017.</li> <li>14. Pettit, K., Swatske, M. E., Gao, F., Salavaggione, L., Gillanders, W. E., Aft, R. L., Monsees, B. S., Eberlein, T. J., Margenthaler, J. A.. The impact of breast MRI on surgical decision-making: are patients at risk for mastectomy?. <i>J Surg Oncol</i>; Dec 1 2009.</li> <li>15. Obdeijn IM, Tilanus-Linthorst MM, Spronk S, van Deurzen CH, de Monye C, Hunink MG, Menke MB.. Preoperative breast MRI can reduce the rate of tumor-positive resection margins and reoperations in patients undergoing breast-conserving surgery. <i>AJR Am J Roentgenol</i>; 2013.</li> <li>16. Lee, J., Jung, J. H., Kim, W. W., Hwang, S. O., Kim, H. J., Park, J. Y., Chae, Y. S., Yang, J. D., Park, H. Y.. The role of preoperative breast magnetic resonance (MR) imaging for surgical decision in patients with triple-negative breast cancer. <i>J Surg Oncol</i>; Jan 2016.</li> <li>17. Hlubocky, J., Bhavnagri, S., Swinford, A., Mitri, C., Rebner, M., Pai, V.. Does the use of pre-treatment MRI change the management of patients with newly diagnosed breast cancer?. <i>Breast J</i>; Nov 5 2017.</li> <li>18. Duygulu G, Oktay A, Bilgen IG, Kapkaç M, Zekioğlu O.. The role of breast MRI in planning the surgical treatment of breast cancer. <i>Diagn Interv Radiol</i>; 2012.</li> </ol> <ol style="list-style-type: none"> <li>a. Downgraded due that initial BCS is not an end outcome, as later women might have received re-excision or a mastectomy depending on the status of operative margins.</li> <li>b. The number of events from the patients recruited in each arm is much lower than the minimum required to have adequate power.</li> <li>c. The intervention (preoperative MRI) was not feasible to be blinded which originated a performance high risk of bias which might have impacted on the surgeon initial planning decision.</li> <li>d. In some cohort studies, the comparison was between arms over different periods of time (no overlapping), and thus potentially introducing a high risk of secular bias.</li> <li>e. The majority of studies reported measurement of association as crude estimates or it had to be calculated from crude numbers.</li> <li>f. There is a high heterogeneity in the estimated effect across the included studies ranging from significant benefit to harm.</li> <li>g. The definition of positive margins was variable across the different clinical centres included (distance from operative margins) this might have introduced a misclassification bias.</li> <li>h. Downgraded due to be a surrogate outcome of disease-free survival.</li> <li>i. A proportion of patients had breast MRI performed after lumpectomy or at re-excision stage which does not directly apply to the clinical pathway of interest.</li> </ol>	
--	---	--

j. The confidence interval of the effect size ranged from significant benefit to harm.

**Accuracy results from included studies**

Study Id	N patients	Diagnostic outcomes	Clinical outcomes
Pilewskie 2012*	352	Multifocal abnormality seen: MM: 15.3%; MRI: 32.6%	
		Bilateral abnormality seen: MM: 6.5%; MRI: 25.7%	Initial BCS: OR 0.71 (0.45 to 1.14).
		Accurate size estimation: MM: 52.1%; MRI: 41.1%	Re-excision rate: OR 0.67 (0.38 to 1.18).
		Size underestimation by 1 cm or more: MM: 13.2%; MRI: 15%	Total mastectomy rate: OR 1.52 (0.95 to 2.41).
		Size overestimated by 1 cm or more: MM: 34.7%; MRI: 43.9%	Treatment change: 15% (11% to 21%)
Hajaj 2017*	122	MRI showed a better histological size correlation compared to MM.	Initial BCS: OR 0.04 (0.01 to 0.17). Re-excision rate: OR 0.55 (0.19 to 1.62).
Davis 2012	218	Identification of additional lesions: 26/154 (16.9%; 10 were biopsy-confirmed and 8 lead to wider lumpectomy).  Detection of invasive contralateral lesions: 4.5% (2 invasive, 5 DCIS)	Initial BCS: OR 0.88 (0.42 to 1.84). Re-excision rate: OR 0.92 (0.48 to 1.78). Total mastectomy rate: OR 1.27 (0.64 to 2.49).

\*the comparison was not made over the same samples as the MRI arm is made of about 60% of the subjects included in the mammography arm.

Adolopment

<ul style="list-style-type: none"> <li>○ Large</li> <li>● Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

## Certainty of evidence

What is the overall certainty of the evidence of effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		The overall certainty of the evidence of effects is very low.
	Adolopment	
<ul style="list-style-type: none"> <li>● Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Add considerations made be the adoloping panel, including the justification for any change in judgment.

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>● Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	No research evidence was identified	The GDG judged that there may be important uncertainty or variability in how much women would value the main outcomes. Better mastectomy and reconstructive surgery may change the values placed on it, but conservative surgery will be preferred by others, depending on the availability of post-surgical radiation therapy.

Adolopment		
<ul style="list-style-type: none"> <li>● Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Add considerations made be the adoloping panel, including the justification for any change in judgment.
<b>Balance of effects</b> Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
Original		
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		The GDG judged that the balance of effects probably favours the comparison.
Adolopment		
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
<b>Resources required</b> How large are the resource requirements (costs)?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
Original		

<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>Median cost of diagnostic/preoperative workup* for women with Stage 0 Breast Cancer.</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #cccccc;"> <th style="text-align: left;">Study ID</th> <th style="text-align: left;">Country</th> <th style="text-align: left;">Year-value</th> <th style="text-align: left;">With MRI</th> <th style="text-align: left;">Without MRI</th> <th style="text-align: left;">Increment</th> <th style="text-align: left;">Quality</th> </tr> </thead> <tbody> <tr> <td colspan="7"><b>Median cost of diagnostic/preoperative workup* (Medicare) US Dollars</b></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td style="text-align: right;"><b>Low<sup>a</sup></b></td> </tr> <tr> <td>Onega2016</td> <td>USA</td> <td>2004–2010</td> <td>\$2627</td> <td>\$1524</td> <td>\$1103</td> <td></td> </tr> </tbody> </table> <p><b>MRI:</b> Magnetic Resonance Imaging. *The time between the initial breast imaging or biopsy within 60 days prior to diagnosis and the primary surgical treatment was defined as the diagnostic/preoperative window. 1) the diagnostic period was defined as 60 days prior to, and including, the diagnosis date; 2) the preoperative period was defined as post diagnosis date to initial surgery date.</p> <p><sup>a</sup> The quality is low due to high risk of bias and indirectness. The study was a retrospective analysis performed in the USA. Medicare data and costs may not be representative of the European setting.</p> <p>The study cohort included women aged 66 yrs. or older at the time of an incident breast cancer diagnosis in 2005–2009 who were enrolled in Medicare for one year before and six months after breast cancer diagnosis (N = 71,193; Stage 0 = 8,533).</p> <p><b>Reference:</b> (Onega T, 2016) Onega T, et al. Costs of diagnostic and preoperative workup with and without breast MRI in older women with a breast cancer diagnosis. BMC Health Serv Res. 2016; 16: 76.</p>	Study ID	Country	Year-value	With MRI	Without MRI	Increment	Quality	<b>Median cost of diagnostic/preoperative workup* (Medicare) US Dollars</b>													<b>Low<sup>a</sup></b>	Onega2016	USA	2004–2010	\$2627	\$1524	\$1103		<p>The GDG judged that the costs are moderate.</p>
Study ID	Country	Year-value	With MRI	Without MRI	Increment	Quality																								
<b>Median cost of diagnostic/preoperative workup* (Medicare) US Dollars</b>																														
						<b>Low<sup>a</sup></b>																								
Onega2016	USA	2004–2010	\$2627	\$1524	\$1103																									
			Adolopment																											
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia																													
<p><b>Certainty of evidence of required resources</b></p> <p>What is the certainty of the evidence of resource requirements (costs)?</p>																														
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>					<b>CONSIDERAZIONI AGGIUNTIVE</b>																								
	Original																													

<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p>The GDG judged that the certainty of the evidence of the required resources is low.</p> <p>US study, representativeness questionable.</p>
Adolopment		
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Non ci sono evidenze su quanto la tecnologia impatti sul percorso di cura a valle della tecnologia
<h3>Cost effectiveness</h3> <p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p>		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
Original		
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ No included studies</li> </ul>	No relevant economic evaluations were identified.	<p>In the UK, for all breast cancers -not particularly for DCIS - 12 months after initial surgery there was no statistically significant difference in HRQoL, as measured by the EQ-5D, between women who underwent MRI vs. no MRI. Also, the economic evaluation did suggest that the MRI arm had a larger mean cost (2010 value) per patient (£5508.40 compared with £5213.50), although the difference was not statistically significant (Turnbull et al., 2010)</p> <p>Net harm, so no cost-effectiveness.</p> <p><b>Reference:</b> (Turnbull et al., 2010)Turnbull LW, et al. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). Health Technol Assess 2010; 14(1).</p>
Adolopment		

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>● Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No research evidence was identified	The GDG judged that equity would probably be reduced because not everybody can have easy access to MRI and the cost is not always covered by health insurance.
	Adolopment	
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Acceptability

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>○ Yes</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	No research evidence was identified	The GDG judged that acceptability varies. Public payers will probably not accept MRI.
	Adolopment	



<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	Non sono state utilizzate evidenze di contesto per l'Italia	Il Panel ritiene che la metodica sia ampiamente accettata dai clinici. Non si ravvisano difficoltà anche da parte delle donne, che anzi spesso richiedono in prima persona tale metodica. Gli erogatori hanno difficoltà a trovare tempi e risorse dedicate.
<b>Feasibility</b> Is the intervention feasible to implement?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	No research evidence was identified	The GDG judged that feasibility varies.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	Riportare da background	Il Panel ritiene che la metodica sia fattibile dal punto di vista dei clinici. Non si ravvisano difficoltà anche da parte delle donne, che anzi spesso richiedono in prima persona tale metodica. Gli erogatori hanno difficoltà a trovare tempi e risorse dedicate.

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLPMENT
PROBLEM	Yes	Yes
DESIRABLE EFFECTS	Trivial	Trivial
UNDESIRABLE EFFECTS	Moderate	Moderate
CERTAINTY OF EVIDENCE	Very low	Very low
VALUES	Important uncertainty or variability	Important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the comparison	Probably favors the comparison
RESOURCES REQUIRED	Moderate costs	Moderate costs

CRITERI	ORIGINAL	ADOLOPMENT
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Low	Low
COST EFFECTIVENESS	Probably favors the comparison	Probably favors the comparison
EQUITY	Probably reduced	Probably reduced
ACCEPTABILITY	Varies	Varies
FEASIBILITY	Varies	Varies

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	<b>Conditional recommendation against the intervention</b> ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	---	---	--	---

## CONCLUSIONI

### Recommendation

In women with histologically confirmed ductal carcinoma in situ (DCIS), the ECIBC's Guidelines Development Group (GDG) suggests not using additional magnetic resonance imaging (MRI) for preoperative planning (conditional recommendation, very low certainty of the evidence).

**Nelle donne con carcinoma duttale in sito confermato (DCIS), il panel suggerisce di non utilizzare una risonanza magnetica addizionale per il planning pre-operatorio (raccomandazione su condizione, certezza delle evidenze molto bassa)**

### Justification

#### Overall justification

Voting was conducted as agreement could not be reached by consensus. The GDG voted: 4 GDG members voted for a conditional recommendation against the intervention, 13 GDG members voted for a strong recommendation against the intervention and one GDG member voted for a conditional recommendation for the intervention. **The majority required for a strong recommendation, 80% votes, was not reached according to ECIBC voting procedures.**

The judgment was based mainly on the evidence on desirable and undesirable effects, the moderate costs, and the fact that the intervention is probably no cost-effective and would probably reduce equity.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects are trivial.

##### *Undesirable Effects*

The GDG judged that the undesirable effects are moderate.

##### *Resources required*

The GDG judged that there are moderate costs associated with the intervention

##### *Cost effectiveness*

According to a UK study, MRI is probably no cost-effective.

##### *Equity*

The GDG judged that the intervention would probably reduce equity.

### Subgroup considerations

Original

Utility in very extended, suspect multifocal, or multiple disease could not be investigated, but the rationale for better morphological has been considered stronger in these cases.  
Low, intermediate and high grade DCIS.

Adolopment

La letteratura più recente include studi osservazionali e randomizzati (in particolare sui CDIS) che mostrano che gli effetti desiderabili potrebbero superare quelli indesiderabili in popolazioni selezionate. Potrebbe essere utile in lesioni molto estese, sospette per multifocalità, multiple che non si sono potute investigare; il rationale per una migliore morfologia è stato considerato più forte nel caso in cui si sospettano lesioni estese, multifocali o multiple. Altro fattore da considerare è il grading (DCIS di basso, intermedio e alto grado): il grading deve essere considerato per valutare i casi di indicazione a MRI ma non è l'unico elemento. Il basso grado diminuisce l'accuratezza (falsi positivi e falsi negativi). Un ultimo caso da valutare è quello del decision-making verso un intervento nipple-sparing vs. no.

## Implementation considerations

Original

None identified.

Adolopment

La raccomandazione contraria all'intervento, in un contesto dove la pratica è diffusa, può risultare problematica stravolgendo abitudini consolidate. Pertanto, bisogna prevedere tempi più lunghi (anche qualche anno) per la corretta implementazione della raccomandazione.

## Monitoring and evaluation

Original

Overuse of MRI especially when there is a very small DCIS mammographically, it is not likely to find a very big one in MRI.

Adolopment

Il panel suggerisce di costruire un indicatore sulla risonanza per monitorare nel tempo se la raccomandazione viene rispettata o meno e la conduzione di survey, ad esempio all'interno dei programmi di screening

## Research priorities

Original

The GDG recommends research on other MRI techniques, especially abbreviated protocols. The ideal design would be RCT but there are problems with feasibility because of numbers and long term outcomes; alternatively observational studies.

The possible utility in specific subgroups (extremely extended, suspect multifocal or multiple lesions) should be investigated.

Adolopment

Il basso livello delle evidenze su cui si è basata la raccomandazione richiede la conduzione di ulteriori studi di buona qualità sugli outcome considerati dal panel. Ulteriori studi ben condotti sono cruciali nel CDIS di grado 3 come precursore del carcinoma invasivo, quanto la MRI ha un vantaggio di sensibilità e di accuratezza del parametro T ed è da investigare se si rifletta su una chirurgia più radicale con minori margini positivi e recidive nell'ottica di prevenzione primaria della malattia infiltrante. Condizione necessaria per la valutazione degli outcome negli studi dedicati è la gestione dei reperti addizionali riscontrati alla RM con verifica istologica nel caso in cui impattino sul trattamento e la comunicazione di tali risultati alla chirurgia.

Dovrebbe essere investigata l'utilità in specifici sottogruppi (molto estesi, sospetto multifocale o lesioni multiple)

Il panel ritiene prioritario lo sviluppo di una raccomandazione italiana sull'utilizzo del MRI sul carcinoma invasivo in quanto si tratta della popolazione verso cui più frequentemente è applicata la metodica nel nostro paese

## REFERENCES SUMMARY

- Schmale I, Liu S, Rayhanabad J, Russell CA, Sener SF. Ductal carcinoma in situ (DCIS) of the breast: perspectives on biology and controversies in current management.. Journal of surgical oncology; 2012.
- Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. CA Cancer J Clin .; 2012.
- Itakura K, Lessing J, Sakata T, Heinzerling A, Vriens E, Wisner D, Alvarado M, Esserman L, Ewing C, Hylton N, Hwang ES.. The impact of preoperative magnetic resonance imaging on surgical treatment and outcomes for ductal carcinoma in situ. Clin Breast Cancer; 2011.
- Pilewskie M, Kennedy C, Shappell C, Helenowski J, Scholtens D, Hansen N, Bethke K, Jeruss J., Karstaedt, P., Khan, S. A.. Effect of MRI on the management of ductal carcinoma in situ of the breast. Ann Surg Oncol; 2013.
- Balleyguier C, Dunant A, Ceugnart L et al. Preoperative Breast Magnetic Resonance Imaging in Women With Local Ductal Carcinoma in Situ to Optimize Surgical Outcomes: Results From the Randomized Phase III Trial IRCIS. J Clin Oncol . 2019 Apr 10;37(11):885-892. doi: 10.1200/JCO.18.00595.
- Lehman CD, Gatsonis C, Romanoff J et al. Association of Magnetic Resonance Imaging and a 12-Gene Expression Assay With Breast Ductal Carcinoma In Situ Treatment. JAMA Oncol. 2019 Jul 1;5(7):1036-1042. doi: 10.1001/jamaoncol.2018.6269.
- Yoon GY, Choi WJ, Kim HH, Cha JH, Shin HJ, Chae EY. Surgical Outcomes for Ductal Carcinoma in Situ: Impact of Preoperative MRI. Radiology. 2020 May;295(2):296-303. doi: 10.1148/radiol.2020191535.
- Sardanelli F, Trimboli RM, Houssami N et al. Magnetic resonance imaging before breast cancer surgery: results of an observational multicenter international prospective analysis (MIPA). Eur Radiol. 2022 Mar;32(3):1611-1623. doi: 10.1007/s00330-021-08240-x.

## QUESITO 2

### Dovrebbe CESM o CEM vs. risonanza magnetica essere utilizzato per diagnosticare donne con cancro alla mammella istologicamente invasivo in aiutare la scelta del trattamento chirurgico?

POPULATION:	donne con cancro invasivo istologicamente confermato
INTERVENTION:	CESM o CEM
COMPARISON:	risonanza magnetica
ANTICIPATED OUTCOMES:	Modifica del trattamento causata dalla CESM (contrast enhancement spectral mammography) o CEM (contrast enhancement mammography) da trattamento conservativo a mastectomia o da mastectomia monolaterale a bilaterale; Proporzioni di re-interventi dopo chirurgia conservativa (re-escissione o conversione a mastectomia); Proporzioni di margini positivi dopo conservativa; Mastectomia; Disease-free survival (inferita da ricorrenze loco-regionali); Qualità della vita (inferita da trattamento conservativo come chirurgia iniziale); Eventi avversi diretti; Outcome di accuratezza diagnostica
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	Il cancro della mammella è la causa di morte più comune tra le donne. In pazienti con un carcinoma mammario invasivo dimostrato da biopsia, in alcuni casi vengono utilizzati metodi di imaging aggiuntivi (cioè definiti dal tipo di tumore) per decidere la terapia chirurgica più appropriata. Attualmente vengono utilizzati due diversi metodi di imaging per misurare l'estensione e anche per dimostrare o escludere multicentricità e multifocalità. Entrambi i metodi condividono il principio di base che il tessuto tumorale è caratterizzato da un maggiore assorbimento dell'agente di contrasto a causa dell'ipervascolarizzazione. Il metodo più utilizzato è la risonanza magnetica (MRI) con potenziamento del gadolinio che non utilizza radiazioni ionizzanti. L'altra tecnica è la mammografia con mezzo di contrasto (CESM o CEM a seconda dei produttori della macchina) che utilizza radiazioni ionizzanti e un agente di contrasto contenente iodio.

**CONFLICT OF INTEREST:**

Sembra importante confrontare entrambi i metodi per quanto riguarda le loro conseguenze sul possibile cambiamento del trattamento chirurgico. La La CESM/CEM è considerata meno costosa, più veloce nell'esecuzione dell'esame e nel tempo di lettura. La risonanza magnetica non utilizza radiazioni ed è attualmente più comunemente disponibile. Entrambi i metodi utilizzano agenti di contrasto con diversi effetti avversi.

Gestione del conflitto di interesse (Col): Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione all'o sviluppo delle raccomandazioni o alla votazione della raccomandazione.

**VALUTAZIONE**

<p><b>Problem</b> Is the problem a priority?</p>		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Breast cancer is the most common cause of death among women. In patients with a biopsy proven invasive breast cancer, additional imaging methods are used in some cases (i. e. defined by tumor type) to decide about the appropriate surgical therapy. At present, two different imaging methods for measuring the extent and also for the proof or exclusion of multicentricity and multifocality are used. Both methods share the underlying principle that tumor tissue has an increased uptake of contrast agent due to hypervascularization. The most widely used method is gadolinium enhanced MRI which does not use ionizing radiation. The contrast agent (gadolinium-containing) is applied during the examination and dynamics of the contrast enhancement are measured in several series to distinguish between benign and malignant findings. Also the shape of the lesion is interpreted. The other technique called CESM (contrast enhanced spectral mammography) uses ionizing radiation and an iodine-containing contrast agent. Two sets of mammography images are taken from each view of each breast after the application of the contrast agent (static examination) a set of low dose images is taken with an energy below the „k-level“ for iodine ( k-level means the applied energy dose (kilovolt) when iodine is visible in x-ray images) and a set of high dose images is taken above the k-level of iodine. The low dose image shows the tissue structures without the already applied contrast agent, whereas the high dose image shows the breast tissue and the contrast agent uptaking lesions. These images are then subtracted and a set of images with only the contrast enhancing lesion is calculated and visualized. Afterwards the size of the lesion, multifocality and multicentricity can be assessed.</p> <p>It seems important to compare both methods regarding the possible change of surgical treatment. CESM is regarded as less expensive, quicker in examination and reading time. MRI does not use radiation and is at present more commonly available. Both methods use contrast agents with different adverse effects.</p>	<p>It seems important to compare both methods regarding the possible change of surgical treatment. CESM is regarded as less expensive, quicker in examination and reading time. MRI does not use radiation and is at present more commonly available. Both methods use contrast agents with different adverse effects.</p> <p>The objective of this question is, if CESM instead of MRI should be used in women with biopsy proven invasive breast cancer for surgical treatment planning.</p>
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	<p>Sebbene la CESM o CEM sia effettuata in varie regioni italiane, allo stato attuale non risulta inserita nel nomenclatore.</p> <p>La disponibilità della tecnologia nei centri di riferimento per il trattamento della mammella è ancora limitata. Al momento i centri che ne hanno la disponibilità la utilizzano principalmente nell'ambito di studi clinici. I pochi centri che la utilizzano nella pratica clinica lo fanno per lo più come estensione di studi clinici già condotti.</p>

## Test accuracy

How accurate is the test?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE																														
<ul style="list-style-type: none"> <li>○ Very inaccurate</li> <li>○ Inaccurate</li> <li>● Accurate</li> <li>○ Very accurate</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Original</p> <p><b>Index lesions</b></p> <table border="1" data-bbox="533 481 1527 616"> <thead> <tr> <th>Outcomes</th> <th>Impact</th> <th>Nº of participants (studies)</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Size correlation</td> <td>Mean absolute difference to pathology: *CESM: 10.1 mm (95%CI 6.95 to 13.23) *MRI: 7.9 mm (95%CI 5.34 to 10.48).</td> <td>(1 OBS)<sup>b</sup></td> <td>⊕⊕○○ LOW<sup>a</sup></td> </tr> </tbody> </table> <p>1. Fallenberg EM1, Schmitzberger FF2, Amer H2, Ingold-Heppner B3, Baileysguier C4, Diekmann F5, Engelken F2, Mann RM6, Renz DM7, Bick U2, Hamm B2, Dromain C4.. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation.. Eur Radiol; 2017 .</p> <p>a. This number includes only ipsilateral breast lesions (multicentric or multifocal).</p> <p>b. Only one study informed this outcome included a total of 52 patients, which make the results highly imprecise.</p> <p><b>Additional lesions (multicentric or multifocal)</b></p> <p><i>Accuracy</i></p> <table border="1" data-bbox="533 938 1527 1369"> <thead> <tr> <th rowspan="3">Test result</th> <th colspan="2">Number of results per 1000 patients tested (95% CI)</th> <th rowspan="3">No of participants (studies)</th> <th rowspan="3">Certainty of the evidence (GRADE)</th> </tr> <tr> <th colspan="2">Prevalence 21%</th> </tr> <tr> <th>Contrast-enhanced spectral mammography</th> <th>MRI</th> </tr> </thead> <tbody> <tr> <td>True positives patients with women with histologically confirmed invasive breast cancer</td> <td>82 (63 to 101)</td> <td>103 (84 to 124)</td> <td rowspan="2">149 (1)<sup>a</sup></td> <td rowspan="2">⊕⊕⊕○ MODERATE<sup>b</sup></td> </tr> <tr> <td></td> <td colspan="2">21 fewer TP in Contrast-enhanced spectral mammography</td> </tr> <tr> <td>False negatives patients incorrectly classified as not</td> <td>128 (109 to 147)</td> <td>107 (86 to 126)</td> <td></td> <td></td> </tr> </tbody> </table>	Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)	Size correlation	Mean absolute difference to pathology: *CESM: 10.1 mm (95%CI 6.95 to 13.23) *MRI: 7.9 mm (95%CI 5.34 to 10.48).	(1 OBS) <sup>b</sup>	⊕⊕○○ LOW <sup>a</sup>	Test result	Number of results per 1000 patients tested (95% CI)		No of participants (studies)	Certainty of the evidence (GRADE)	Prevalence 21%		Contrast-enhanced spectral mammography	MRI	True positives patients with women with histologically confirmed invasive breast cancer	82 (63 to 101)	103 (84 to 124)	149 (1) <sup>a</sup>	⊕⊕⊕○ MODERATE <sup>b</sup>		21 fewer TP in Contrast-enhanced spectral mammography		False negatives patients incorrectly classified as not	128 (109 to 147)	107 (86 to 126)			<p><b>Digital mamography (additional lesions)</b> Sensitivity: 17% Specificity: 95% (Fallenberg 2017)</p> <p><b>Digital mamography (index size correlation)</b> Mean absolute difference: 12.22 mm (95%CI 8.97 to 15.47). (Fallenberg 2017)</p>
Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)																													
Size correlation	Mean absolute difference to pathology: *CESM: 10.1 mm (95%CI 6.95 to 13.23) *MRI: 7.9 mm (95%CI 5.34 to 10.48).	(1 OBS) <sup>b</sup>	⊕⊕○○ LOW <sup>a</sup>																													
Test result	Number of results per 1000 patients tested (95% CI)		No of participants (studies)	Certainty of the evidence (GRADE)																												
	Prevalence 21%																															
	Contrast-enhanced spectral mammography	MRI																														
True positives patients with women with histologically confirmed invasive breast cancer	82 (63 to 101)	103 (84 to 124)	149 (1) <sup>a</sup>	⊕⊕⊕○ MODERATE <sup>b</sup>																												
	21 fewer TP in Contrast-enhanced spectral mammography																															
False negatives patients incorrectly classified as not	128 (109 to 147)	107 (86 to 126)																														

having women with histologically confirmed invasive breast cancer	21 more FN in Contrast-enhanced spectral mammography			
True negatives patients without women with histologically confirmed invasive breast cancer	743 (624 to 782)	695 (553 to 758)	149 (1) <sup>a</sup>	⊕⊕⊕○ MODERATE <sup>b</sup>
	48 more TN in Contrast-enhanced spectral mammography			
False positives patients incorrectly classified as having women with histologically confirmed invasive breast cancer	47 (8 to 166)	95 (32 to 237)		
	48 fewer FP in Contrast-enhanced spectral mammography			

- a. The numbers represent the number of lesions included in the analysis instead of the number of patients.
- b. The results are imprecise due to the low number of lesions/patients included.

**Detection rate**

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
Additional findings (multicentric and multifocal)	Detection rate (over number of patients): *CESM: 17% (95%CI: 8% to 30%) *MRI 29% (95%CI: 17% to 43%)	(1 OBS) <sup>1</sup>	⊕⊕○○ LOW <sup>1,2</sup>

1. Jochelson MS, Dershaw DD, Sung JS, Heerdt AS, Thornton C, Moskowitz CS, Ferrara J, Morris EA. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma. Radiology; 2013 .

- a. One study (Jochelson) did not include follow-up for patients and then for additional lesions there was a risk of confirmation bias as small resection was provided if no evidence of additional findings.
- b. Only one study reported detection rate over a low number of patients (n=52), and did not include a clinical follow-up (Jochelson).

**False positive**

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
False positive findings	Number of false positive findings (per patients): *CESM: 4% (95% CI 0% to 13%) *MRI: 15% (95%CI 7% to 28%), <sup>a</sup>	(1 OBS) <sup>1</sup>	⊕⊕○○ LOW <sup>1</sup>

1. Fallenberg EM1, Schmitzberger FF2, Amer H2, Ingold-Heppner B3, Balleyguier C4, Diekmann F5, Engelken F2, Mann RM6, Renz DM7, Bick U2, Hamm B2, Dromain C4. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation. Eur Radiol; 2017.

- a. Only on study informed this outcome with 70 index lesions from 155 patients, the results were imprecise and therefore it was considered as a serious concern on this domain.

Adolopment



<ul style="list-style-type: none"> <li>○ Very inaccurate</li> <li>○ Inaccurate</li> <li>● Accurate</li> <li>○ Very accurate</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Vedi appendice su update europeo, sono stati aggiunti 5 studi. Non ci sono variazioni nel giudizio
--	--	--

## Desirable Effects

How substantial are the desirable anticipated effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>● Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No evidence identified for clinical outcomes.	<p>Considering the less false positive with CESM, GDG agreed that the desirable effects are moderate.</p> <p><b>Adverse reactions to contrast material.</b> Iodinated contrast used in CESM tests is less hazardous than the gadolinium contrast used in MRI. Both, the differences in the frequency of adverse events, as well as the overall frequency, are small (Lewin, 2018).</p>
	Adolopment	
<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>● Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	<p>Il Panel ritiene che sia per facilità di esecuzione che per accuratezza diagnostica risulti sostanzialmente sovrapponibile alla RMN.</p> <p>Vedi appendice su update europeo, sono stati aggiunti 5 studi. Non ci sono variazioni nel giudizio</p> <p>INTEGRARE LA PARTE SU PERICOLOSITA</p>

## Undesirable Effects

How substantial are the undesirable anticipated effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	

<ul style="list-style-type: none"> <li><input type="radio"/> Large</li> <li><input type="radio"/> Moderate</li> <li><input checked="" type="radio"/> Small</li> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	No evidence identified for clinical outcomes.	<p>GDG considered as undesirable effects the higher number of false negatives with CESM, the higher radiation dose and possible impact on kidney and thyroid.</p> <p>As consensus was not reached, voting was conducted among the GDG members to judge undesirable effects: 10 members voted "small", 7 members voted "moderate".</p>
--	---	---

Adolopment
------------

<ul style="list-style-type: none"> <li><input type="radio"/> Large</li> <li><input type="radio"/> Moderate</li> <li><input checked="" type="radio"/> Small</li> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Vedi appendice su update europeo, sono stati aggiunti 5 studi. Non ci sono variazioni nel giudizio
--	--	--

<h3 style="margin: 0;">Certainty of the evidence of test accuracy</h3> <p style="margin: 0; font-size: small;">What is the overall certainty of the evidence of test accuracy?</p>		
--	--	--

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
---------	---------------------------------	---------------------------

Original
----------

<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>		The certainty of the evidence is low.
---	--	---------------------------------------

Adolopment
------------

<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

## Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	No research evidence was identified	
	Adolopment	
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	Non sono state considerate evidenze di contesto per l'Italia	Add considerations made be the adoloping panel, including the justification for any change in judgment.

## Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	No research evidence was identified	A systematic review about the role of preoperative MRI versus no-MRI in all breast cancer histology suggested an unfavourable harm-benefit ratio for routine use of preoperative MRI in the management of breast cancer (MRI significantly increased mastectomy rates - adjusted OR, 1.51, P < 0.001-) (Houssami 2013). [see recommendation on peri-operative MRI]
	Adolopment	
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	Non sono state considerate evidenze di contesto per l'Italia	

## Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	

<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	No research evidence was identified	
Adolopment		
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
<b>Certainty of effects</b> What is the overall certainty of the evidence of effects of the test?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
Original		
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>		<p>Overall certainty not determined, the GDG focused on certainty of the evidence about test accuracy.</p> <p>This is true for both the index and the comparison test.</p>
Adolopment		
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
<b>Values</b> Is there important uncertainty about or variability in how much people value the main outcomes?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
Original		
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	No research evidence was identified	<p>The GDG judged that there may be possibly important uncertainty or variability in how much women would value the main outcomes.</p> <p>Better mastectomy and reconstructive surgery may change the values placed on it, but conservative surgery will be preferred by others.</p>

As consensus was not reached, voting was conducted among the GDG members to judge values: 12 members voted “possibly important”, 5 members voted “probably no important”, 1 member voted “no important uncertainty”.

			As consensus was not reached, voting was conducted among the GDG members to judge values: 12 members voted “possibly important”, 5 members voted “probably no important”, 1 member voted “no important uncertainty”.
	Adolopment		
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia		
<b>Balance of effects</b>			
Does the balance between desirable and undesirable effects favor the intervention or the comparison?			
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>		<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original		
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>			As consensus was not reached, voting was conducted among the GDG members to judge the balance of effects: 9 members voted “probably favours the intervention”, 8 members voted “does not favour either”, 1 member voted “probably favours the comparison”.
	Adolopment		
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia		

## Resources required

How large are the resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>● Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>CESM is less expensive</b> than MRI due to:</p> <p><b>1) Lower equipment cost.</b> The price of an MRI machine is 815,000 USD (including coils, annual maintenance, and injector). The cost of a 2D mammography unit with CESM is 435,000 USD (with annual maintenance and injector) (Patel BK, 2017).</p> <p><b>2) Shorter examination time:</b> CESM acquisition lasts approximately 10 minutes, whereas MRI requires 30–60 minutes. As in MRI, an additional 10–15 minutes is required for contrast injection (Patel BK, 2017).</p> <p><b>3) Sedation is not needed.</b> Potential savings for the 1–15% of patients who need sedation during MRI because of associated claustrophobia (Patel BK, 2017).</p> <p><b>4) Lower reading time.</b> MRI requires 3–10 minutes for interpretation, whereas CESM study can be interpreted in 1–2 minutes (Patel BK, 2017).</p>	<p>The device for CESM is relatively inexpensive, but it is not available on all devices.</p> <p>MRI machine, its contract agent and breast dedicated coils are more expensive than CESM.</p> <p>More training required for MRI.</p> <p>The GDG judged that there are moderate savings with CESM.</p>
	Adolopment	
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>● Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	La tecnologia può essere acquisita come estensione applicabile a mammografi già installati, con una spesa di poche decine di migliaia di euro.

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Low certainty of the evidence due to risk of bias and indirectness. The study of Patel et al (Patel BK, 2017) was a descriptive study that did not consider the consequences of the test. The reported costs were observed in the USA in 2015 only for the Medicare perspective.	
	Adolopment	

<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Non ci sono studi europei e sull'impatto "a valle" del test, ma non c'è incertezza sulla direzione della riduzione dei costi
--	--	--

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No relevant economic evaluations were identified.	
	Adolopment	
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Nonostante l'assenza di studi è probabile che favorisca la CESM sulla base del balance of effects e dei costi

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	No research evidence was identified	On the basis of availability and the policy of reimbursement. E.g. in Germany a preoperative MRI is not reimbursed; CESM may be cheaper.

	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Reduced</li> <li><input type="radio"/> Probably reduced</li> <li><input type="radio"/> Probably no impact</li> <li><input type="radio"/> Probably increased</li> <li><input type="radio"/> Increased</li> <li><input checked="" type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	La distrbuzione della CESM è disomogenea sul territorio, così come la presenza delle MRI. Il problema di equità potrebbe essere sovrapponibile per le due tecnologie ma molto variabile da regione a regione e comunque dipendente anche dal problema di tariffazione della CESM
<h2 style="margin: 0;">Acceptability</h2> <p style="margin: 0;">Is the intervention acceptable to key stakeholders?</p>		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	No research evidence was identified	<p>CESM may be more acceptable because of the invasiveness but others may not want more radiation. In case of an already diagnosed breast cancer the radiation dose on the breast with the cancer is negligible, because there will be postsurgical radiation therapy anyway in almost all cases.</p> <p>Direct undesirable consequences of MRI may be less important if the supposed diseases are more severe.</p> <p>CESM is less expensive (policy makers) but more referrals to other centers because of availability but this depends on the availability.</p> <p>Patients have to wait longer for MRI making CESM more acceptable (this may affect all stakeholders).</p> <p>As consensus was not reached, voting was conducted among the GDG members to judge acceptability: 12 members voted "probably yes", 3 members voted "yes", 2 members voted "varies", 1 member voted "probably no".</p>
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Si evidenzia che la CESM appare meglio accettata da parte delle donne rispetto alla RMN (indipendenza dal ciclo mestruale, obesità, claustrofobia, ...)



## Feasibility

Is the intervention feasible to implement?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No research evidence was identified	<p>Many existing mammography units can be upgraded to include CESM capabilities. CESM can be implemented without the space requirements of an MRI magnet. CESM can be used in women with pace makers, MRI not. As consensus was not reached, voting was conducted among the GDG members to judge feasibility: 12 members voted "probably yes", 4 members voted "yes", 2 members voted "varies".</p>
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	<p>La fattibilità appare migliore rispetto all'esecuzione di una RMN.</p> <p>La CESM non può essere eseguita in ambito ambulatoriale laddove non vi sia la presenza di un anestesista, in quanto è necessaria la gestione delle possibili reazioni allergiche gravi.</p> <p>Viene utilizzata la stessa apparecchiatura per la mammografia, e il mdc è approvato per questo uso. La tecnologia può essere acquisita come estensione applicabile a mammografi già installati, con una spesa di poche decine di migliaia di euro. I mammografi devono però essere di ultima generazione e non tutte le compagnie hanno sviluppato tale tecnologia.</p> <p>La disponibilità di tali mammografi è però piuttosto diffusa in Italia.</p>

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLOPMENT
PROBLEM	Yes	Yes
TEST ACCURACY	Accurate	Accurate
DESIRABLE EFFECTS	Moderate	Moderate
UNDESIRABLE EFFECTS	Small	Small

<b>CRITERI</b>	<b>ORIGINAL</b>	<b>ADOLOPMENT</b>
<b>CERTAINTY OF THE EVIDENCE OF TEST ACCURACY</b>	Low	Low
<b>CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS</b>	No included studies	No included studies
<b>CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS</b>	No included studies	No included studies
<b>CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT</b>	No included studies	No included studies
<b>CERTAINTY OF EFFECTS</b>	No included studies	No included studies
<b>VALUES</b>	Possibly important uncertainty or variability	Possibly important uncertainty or variability
<b>BALANCE OF EFFECTS</b>	Probably favors the intervention	Probably favors the intervention
<b>RESOURCES REQUIRED</b>	Moderate savings	Moderate savings
<b>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</b>	Low	Low
<b>COST EFFECTIVENESS</b>	No included studies	No included studies
<b>EQUITY</b>	Varies	Varies
<b>ACCEPTABILITY</b>	Probably yes	Probably yes
<b>FEASIBILITY</b>	Probably yes	Probably yes

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
---	--	---	---	---

## CONCLUSIONI

Original

### Recommendation

In women with histologically confirmed invasive breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests using contrast-enhanced spectral mammography (CESM) over magnetic resonance imaging (MRI) to assist in surgical treatment planning (conditional recommendation, low certainty of the accuracy evidence).

### Justification

The differences in health benefits and harms were small but tended to favour CESM, other criteria may be more important such as costs and acceptability and feasibility issues.

Adolopment

### Recommendation

**Nelle donne con cancro della mammella invasivo istologicamente confermato, il panel suggerisce di utilizzare la CESM rispetto alla risonanza magnetica a supporto del planning del trattamentop (raccomandazione su condizione, bassa certezza nelle evidenze di accuratezza).**

### Justification

La raccomandazione è dovuta ai vantaggi che la CESM dimostra in termini di vantaggi di implementazione, anche a fronte di scarse evidenze in particolare rispetto all'impatto clinico

### Subgroup considerations

Original

E.g. women with Pace Makers who can't have an MRI.

Pre-menopausal women should be informed about the feasibility of carrying out the MRI in the post-ovulation phase of their cycle

Adolopment

A differenza della MRI, la CESM è utilizzabile anche nei portatori di pacemaker e non risente della fase del ciclo.

È necessario definire in quali condizioni è indicata CESM e in quali sia indicata MRI

Studi recenti mostrano che la CESM è alternativa valida alla MRI anche nei carcinomi lobulari (Lobbes M et al) e nelle pazienti con protesi

Per quanto riguarda lo studio del burden linfonodale, la MRI non è la metodica di scelta pertanto la CESM anche in questo caso non è inferiore alla MRI

### Implementation considerations

Original

The GDG discussed MRI being currently the test of choice for certain women and settings. Use of CESM will reduce the bottle neck of MRI availability for these patients (would be urgent MRIs given that they have to be done before surgery).

As for any conditional recommendation values and preferences and shared decision making (possibly decision aids) should be taken into account.

#### Adolopment

La risonanza è attualmente il test di scelta per alcune categorie di donne e di setting. L'utilizzo della CESM ridurrebbe il collo di bottiglia della disponibilità della MRI per queste donne, rendendo disponibili più risorse in caso di necessità.

I valori, le preferenze e lo shared decision making (possibilmente con l'uso di decision aids) devono essere presi in considerazione in quanto la raccomandazione è solo "condizionale".

Il giudizio sull'effettiva implementazione della tecnologia dovrebbe essere affidato ad agenzie regolatorie

## Monitoring and evaluation

#### Original

Overuse of CESM/MRI should be monitored (increase in referral because of easy of conduct of test).

#### Adolopment

La CESM/RMN hanno solo poche indicazioni specifiche, pertanto ne va monitorato l'uso inappropriato.

## Research priorities

#### Original

Better research on accuracy and patient impact.

Subtypes of breast cancer with CESM especially regarding the likelihood of multicentricity or multifocality.

#### Adolopment

La letteratura più recente evidenzia solo piccole differenze rispetto alla RMN. La CESM appare infatti più specifica e meno sensibile nella maggior parte degli studi, con alcune eccezioni.

La ricerca sull'accuratezza e sull'impatto sulle pazienti risulta pertanto una priorità.

Sono necessari studi clinici "di uso".

## REFERENCES SUMMARY

1.Lobbes MBI, Neeter LMFH, Raat F, Turk K, Wildberger JE, van Nijnatten TJA, Nelemans PJ. The performance of contrast-enhanced mammography and breast MRI in local preoperative staging of invasive lobular breast cancer. Eur J Radiol. 2023 Jul;164:110881

2. Hogan MP, Amir T, Mango VL, Morris EA, Jochelson MS. Feasibility of contrast-enhanced mammography in women with breast implants. Clin Imaging. 2023 Jan;93:31-33. doi: 10.1016/j.clinimag.2022.10.012. Epub 2022 Oct 27.

## QUESITO 3

**Dovrebbe tomosintesi digitale della mammella vs. mammografia diagnostica essere utilizzato per diagnosticare cancro della mammella in donne richiamate per lesioni sospette alla mammografia di screening?**

<b>POPULATION:</b>	Donne richiamate allo screening per lesione sospetta
<b>INTERVENTION:</b>	tomosintesi digitale della mammella
<b>COMPARISON:</b>	mammografia diagnostica
<b>PURPOSE OF THE TEST:</b>	Valutare se la DBT è più utile delle proiezioni aggiuntive alla mammografia quando viene identificato un sospetto alla mammografia di screening
<b>ANTICIPATED OUTCOMES:</b>	<p>i) Outcome clinici:</p> <ul style="list-style-type: none"> <li>- Qualità della vita.</li> <li>- Mortalità per cancro della mammella</li> <li>- Cancro radio-indotto</li> </ul> <p>ii) Outcome di accuratezza diagnostica*</p> <ul style="list-style-type: none"> <li>- Sensibilità</li> <li>- Specificità</li> </ul>
<b>SETTING:</b>	Italia
<b>PERSPECTIVE:</b>	Popolazione (Servizio Sanitario Nazionale)
<b>BACKGROUND:</b>	La tomosintesi (DBT) è una tecnica mammografica modificata che acquisisce immagini di proiezione a basso dosaggio del seno con angolature differenti. Questo supera l'effetto della sovrapposizione del tessuto mammario, che è una delle limitazioni della mammografia digitale (FFDM). Quando si sospetta la presenza di una lesione sottostante durante lo screening con FFDM, la donna viene richiamata per una valutazione ulteriore che potrebbe consistere, tra le altre cose, in compressione localizzata, magnificazione, etc. Il richiamo comporta costi elevati e causa ansia, non solo prima della valutazione ma anche durante il periodo precedente alla successiva mammografia di screening (nonostante la persona abbia ricevuto un risultato finale negativo nella valutazione). La sovrapposizione dei tessuti normali in FFDM può produrre caratteristiche sulla mammografia che sono sospette per icanro, portando al richiamo per ulteriori test. La DBT potrebbe evitare questa sovrapposizione di tessuti normali e quindi dare al radiologo maggiore certezza sul tipo e le caratteristiche della lesione sospetta. Sulla base del tipo di lesioni sospette, sono state identificate le seguenti sottopopolazioni: distorsioni architettoniche, masse, densità asimmetriche, calcificazioni. I risultati delle immagini sono stati considerati negativi quando BI-RADS 1-2, positivi BI-RADS 3-4-5. Si consiglia di evitare il BI-RADS 3 in screening. Il BI-RADS 0, che indica di per sé una valutazione ulteriore, è stato considerato anche come positivo. Il test di riferimento è l'istologia (chirurgia o biopsia) o il follow-up a lungo termine
<b>CONFLICT OF INTEREST:</b>	<u>Gestione del conflitto di interesse (CoI)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Original				
Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
Adolopment				
Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○

## CONCLUSIONI

Original

### Recommendation

The ECIBC's Guidelines Development Group (GDG) suggests using digital breast tomosynthesis (DBT) over diagnostic mammography projections in women at average risk for breast cancer recalled for suspicious lesions at mammography screening (conditional recommendation, moderate certainty of the test accuracy data).

### Justification

The GDG agreed the recommendation by consensus.

It is a conditional recommendation mainly due to the availability of the devices. In addition, despite moderate certainty in the high accuracy of the test results, and a balance that probably favours DBT, there are concerns about the associated moderate costs, increased training needed to correctly use this technology, absence of cost-effectiveness data and feasibility of its implementation.

Adolopment

### Recommendation

**Il panel suggerisce di utilizzare la tomosintesi rispetto alle proiezioni aggiuntive mammografiche nelle donne a medio rischi o di cancro della mammella richiamate ad approfondimento per sospetto alla mammografia di screening (raccomandazione su condizione, certezza moderata delle evidenze di accuratezza)**

### Justification

### Subgroup considerations

Original

The GDG agreed that this recommendation applies to both subgroups of patients examined, those with calcified lesions and those with non calcified lesions.

Adolopment

La raccomandazione si applica sia in caso di calcificazione che no.

### Implementation considerations

Original

None were considered by GDG.

Adolopment

Nessuna

### Monitoring and evaluation

Original

Quality control procedures and quality standards should be further developed. Standards should be developed in particular for the image quality of synthesised 2D images from the tomosynthesis technology.

#### Adolopment

Il Panel concorda sulla necessità di standardizzare le immagini.

## Research priorities

#### Original

Ultrasound is often included in the management of assessment after a positive finding in screening mammography. Further researh should be conducted exploring which subgroups would avoid ultrasound after DBT- additional projections, as well as which lesions (usually masses) are assessed with ultrasound instead of additional projections/DBT.

The use of DBT in high mammographic breast density should be explored, that is, whether or not accuracy results are affected by breast density.

Members of the GDG raised the question of whether the evidence discussed applies to repeated assessments too, but there was no agreement in the GDG if this is a research priority.

Whether or not to use one or two views for tomosynthesis in assessment should be explored.

#### Adolopment

Esistono diversi campi di ricerca che meritano un approfondimento; oltre a quelli già riportati dal Panel europeo, anche l'utilizzo della tomosintesi a campo aperto o con compressione mirata; in fase di approfondimento è difficile definire un algoritmo sequenziale di utilizzo delle metodiche in quanto ogni caso può richiedere un percorso diagnostico personalizzato; pertanto, questa tematica andrebbe sviluppata in studi dedicati.

L'ecografia è spesso inclusa nella gestione della valutazione dopo un positivo allo screening. Dovrebbero essere condotte ulteriori ricerche per esplorare quali sottogruppi potrebbero evitare l'ecografia dopo le proiezioni aggiuntive di DBT, nonché quali lesioni (solitamente masse) vengono valutate con l'ecografia invece di proiezioni aggiuntive/DBT.

Dovrebbe essere esplorato l'uso di DBT in presenza di una densità mammaria elevata, ovvero se i risultati di accuratezza sono influenzati dalla densità del seno. Dovrebbe essere esplorato se utilizzare una o due proiezioni per la tomosintesi.

## REFERENCES SUMMARY

1. Michell MJ, Iqbal A, Wasan RK, Evans DR, Peacock C, Lawinski CP, Douiri A, Wilson R, Whelehan P.. A comparison of the accuracy of film-screen mammography, full-field digital mammography, and digital breast tomosynthesis. Clin Radiol; 2012.
2. Brett J, Austoker J. Women who are recalled for further investigation for breast screening: Psychological consequences 3 years after recall and factors affecting re-attendance.. Journal of Public Health Medicine; 2001.
3. Michell MJ, Batohi B.. Role of tomosynthesis in breast imaging going forward.. Clinical Radiology; 2018.
4. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al.. ACR BI-RADS® Atlas Breast Imaging Reporting and Data System, Reston VA, American College of Radiology. 2013.

## QUESITO 4

### Dovrebbe agobiopsia mammaria vs. citologia da aspirato ad ago sottile essere utilizzato per diagnosticare cancro della mammella in donne con lesioni sospette alla mammografia?

POPULATION:	donne con lesioni sospette alla mammografia
INTERVENTION:	agobiopsia mammaria
COMPARISON:	citologia da aspirato ad ago sottile
PURPOSE OF THE TEST:	Sostituzione
LINKED TREATMENTS:	Trattamenti per il cancro della mammella
ANTICIPATED OUTCOMES:	Sensibilità, specificità, eventi avversi, numero di biopsie ripetute, planning errato dell'intervento chirurgico, qualità della vita

<b>SETTING:</b>	Italia
<b>PERSPECTIVE:</b>	Popolazione (Servizio Sanitario Nazionale)
<b>BACKGROUND:</b>	<p>Nella valutazione delle donne che hanno una mammografia di screening sospetta, l'obiettivo è quello di minimizzare la necessità di rimozione chirurgica di lesioni non clinicamente rilevanti e, contemporaneamente, di ridurre il rischio di perdere una lesione clinicamente rilevante. L'unico modo per ridurre significativamente entrambi i rischi è quello di effettuare una valutazione citologica o istopatologica pre-chirurgica delle lesioni sospette. Attualmente, ci sono due metodi non operatori per ottenere campioni di una lesione al seno: la citologia a aspirazione con ago e la core biopsy. A seconda del tipo di lesione, la biopsia ad ago core può essere eseguita sotto guida ecografica o stereotattica, utilizzando aghi di calibro variabile e tecnologia di aspirazione a vuoto, quando indicato.</p> <p>Le masse e le densità asimmetriche rappresentano circa il 30-40% delle lesioni sospette al seno che vengono campionate per la valutazione citologica/istologica nella popolazione di screening mammografico e circa il 70% delle lesioni campionate nelle donne sintomatiche. Il prelievo di questi tipi di lesioni è di solito meno impegnativo rispetto ad altri reperti radiologici come le calcificazioni perché queste sono di solito visibili all'ecografia.</p> <p>Le distorsioni architettoniche costituiscono circa il 7% delle lesioni sottoposte a campionamento citologico/istologico nello screening. In questa popolazione, il campionamento può essere più impegnativo rispetto alle masse, perché i limiti delle lesioni non sono chiaramente definiti e le lesioni potrebbero non essere visibili all'ecografia.</p> <p>Le calcificazioni costituiscono circa il 30% delle lesioni sottoposte a campionamento citologico/istologico nello screening. Ottenere un prelievo rappresentativo tende ad essere più difficile e costoso poiché le calcificazioni non si riescono a palpare e raramente sono visibili all'ecografia. Nonostante ciò, le calcificazioni possono essere associate al carcinoma in situ e invasivo. Il rischio complessivo per diagnosi in una donna con calcificazioni è di circa il 6%.</p> <p>La citologia aspirativa con ago sottile (FNAC) è un metodo diagnostico minimamente invasivo eseguito con un ago di 20-25 gauge. Questa procedura può fornire una diagnosi rapida (meno di 30 minuti) e ridurre il dolore legato alla biopsia grazie all'uso di un ago di dimensioni più piccole. Fattori come la dimensione del tumore (piccole lesioni), il tipo di lesione sospetta alla mammografia (in particolare in caso di calcificazioni) e l'uso del metodo a mano libera senza alcuna guida radiologica influenzano il tasso di risultati non conclusivi. L'architettura di una lesione non è preservata in FNAC, non è possibile distinguere con precisione il carcinoma in situ dal carcinoma invasivo. In considerazione di ciò, i campioni FNAC non sono adatti per la valutazione del tipo istologico, del grado e del profilo di biomarcatori tumorali. È importante avere accesso a queste informazioni preoperatorie per prendere decisioni riguardo al tipo di intervento chirurgico e alla chemioterapia neoadiuvante per il trattamento del cancro al seno invasivo.</p> <p>La core biopsy ad ago (NCB) comporta il campionamento della lesione sospetta con un ago di dimensioni comprese tra 8G e 11G per i sistemi a aspirazione sottovuoto e tra 12G e 18G per altri tipi di biopsia. Ad oggi la core biopsy è considerata una procedura standard per la valutazione della maggior parte delle lesioni al seno. In alcuni paesi, la FNAC viene ancora utilizzata come primo passo del campionamento a causa della facilità di accesso e del costo inferiore. L'analisi patologica del campione di tessuto prelevato da NCB o la core biopsy sottovuoto (VANCB) consente la valutazione delle caratteristiche cellulari e architettoniche di una lesione. Ciò consente di distinguere il carcinoma in situ dal carcinoma invasivo e di determinare informazioni biologiche prognostiche e predittive, compreso il tipo istologico, il grado e lo stato del recettore dei biomarcatori. Ciò migliora notevolmente il processo decisionale preoperatorio e di gestione. L'uso della biopsia tissutale è stato correlato a un dolore leggermente maggiore, al rischio di ematoma dovuto alle dimensioni dell'ago più grandi e, in rare occasioni, a un aumentato rischio di infezione rispetto alla FNAC.</p> <p>Anche se il ruolo della FNAC è discutibile a causa dei tassi di inadeguato e delle limitazioni nella caratterizzazione e nel profilo di un tumore come descritto in precedenza, può essere utile nella valutazione di alcuni tipi di dubbio diagnostico. Nel decidere di utilizzare la FNAC o la NCB, è importante considerare le caratteristiche cliniche e di imaging della lesione e la capacità o meno di visualizzare la lesione all'ecografia.</p> <p>La biopsia a cielo aperto è una procedura chirurgica che è diagnostica e frequentemente terapeutica allo stesso tempo. È il metodo più invasivo per ottenere una diagnosi e viene eseguito solo quando non è stato possibile raggiungere una diagnosi utilizzando le tecniche non invasive descritte in precedenza.</p> <p>Alcuni autori hanno ipotizzato che il prelievo di cellule o tessuti possa aumentare il rischio di metastasi a causa dello spostamento delle cellule cancerose. Sebbene esista un ampio consenso sui benefici della valutazione citologica e/o istologica prima dell'intervento chirurgico, questa questione è stata affrontata nella revisione sistematica con la valutazione di eventuali prove indirette o ricerche correlate.</p>
<b>CONFLICT OF INTEREST:</b>	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Original				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention



○	○	○	○	●
Adolopment				
Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●

## CONCLUSIONI

Original

### Recommendation

In individuals with suspicious breast lesions (including mass lesions, asymmetric breast density, calcifications and/or architectural distortions) in mammography, the ECIBC's Guidelines Development Group recommends needle core biopsy over fine needle aspiration cytology to diagnose breast cancer (strong recommendation, moderate certainty in the evidence).

**Negli individui con lesioni della mammella sospette (tra cui masse, densità asimmetriche, calcificazioni e/o distorsioni architetturali) alla mammografia, il panel raccomanda la core biopsy invece della citologia ad ago sottile per la diagnosi di cancro della mammella (raccomandazione forte, certezza moderata nelle evidenze)**

### Justification

#### Overall justification

#### Detailed justification

##### *Desirable Effects*

The GDG judged that there are large desirable effects of the intervention (NCB) due to the increased number of true positives and true negatives and less false positives and false negatives.

##### *Undesirable Effects*

The GDG judged that the undesirable effects of the intervention, including bleeding and pain, are trivial.

##### *Balance of effects*

The GDG judged that the balance of effects favours NCB because the desirable health effects considerably outweigh the undesirable ones.

##### *Resources required*

The GDG judged that the additional resources required for NCB are negligible in view of its increased effectiveness.

##### *Equity*

The GDG judged that the strong recommendation for the use of NCB would result in increased equity within countries that currently do not routinely use NCB in all healthcare centres.

### Subgroup considerations

Original

Initially, the GDG had divided this question in three according to different types of subpopulations (i. mass lesions and/or asymmetric density, ii. architectural distortions and iii. calcifications) but as the literature search did not find studies giving information for the relevant outcomes separately for the two subpopulations, it was merged.

Adolopment

Il Panel concorda con la considerazione europea, ovvero che le sottopopolazioni nelle quali era originariamente diviso il quesito sono da raggruppare in un'unica popolazione avendo risultati simili. Si sottolinea che profilo molecolare ottenuto sulla core needle biopsy rappresenta ad oggi il gate keeper su lesioni tumorali anche di un cm (HER2 enriched e tripli negativi).

## Implementation considerations

Original

The GDG noted that FNAC may have utility in other medical conditions or contexts (e.g. FNAC of axilla lymph nodes) and as such reinforces that this recommendation applies only to the population addressed in this question; the GDG did not consider other populations.

The GDG noted that there may be resistance to implementation in certain settings where providers are using FNAC over NCB. The concomitant issue is that if we are monitoring the move to NCB you should also monitor other histopathology tests that are implemented in parallel to NCB.

Adolopment

L'implementazione di questa raccomandazione merita particolare attenzione perchè la prassi nella situazione italiana non è ancora congruente con la raccomandazione.

## Monitoring and evaluation

Original

The GDG notes that the Quality Assurance Development Group should be alerted to this recommendation and consider monitoring and evaluation issues for this question. Monitoring the positive predictive value of the intervention may be helpful for quality assurance.

The GDG notes that centres currently performing FNAC instead of NCB (for the population in this question) should be monitored for the implementation of this intervention.

Adolopment

Vista la prassi difforme in Italia è necessario monitorare l'applicazione della raccomandazione tramite indicatori ad hoc. Si raccomandano:

- i. proporzione di approfondimenti con FNAC sul totale di approfondimenti con prelievo di tessuto (FNAC+CNB+VABB).
- ii. proporzione di casi operati con solo accertamento citologico pre-operatorio
- iii. proporzione di casi di carcinoma mammario (invasivo, intraduttale) con una diagnosi micro-istologica preoperatoria (B5) (v. definizione nel novero degli indicatori Senonetwork)

## Research priorities

Original

Research on how to communicate more effectively with women so they can make an informed choice, in this assessment stage of breast cancer, for NCB vs FNAC, based on this recommendation. This is particularly important in settings where FNAC is still used.

Adolopment

Il panel segnala l'utilità di rivalutare il ruolo della rose citology in progetti di ricerca.

## REFERENCES SUMMARY

1. Venkatesan A, Chu P, Kerlikowske K, Sickles EA, Smith-Bindman R.. Positive predictive value of specific mammographic findings according to reader and patient variables. Radiology; 2009.
2. Wilkinson S, Perry R, Blanchard K, Linsell L.. Effectiveness of a three-day communication skills course in changing nurses' communication skills with cancer/palliative care patients: a randomised controlled trial.. Palliative Medicine; 2008.

## QUESITO 5

### Dovrebbe agobiopsia a guida stereotassica o VABB a guida stereotassica vs. agobiopsia ecoguidata o VABB ecoguidata essere utilizzato per diagnosticare la presenza del cancro alla mammella in donne positive per calcificazioni al seno?

POPULATION:	Donne con sospetto cancro della mammella, definito dalla presenza di calcificazioni in una recente mammografia
INTERVENTION:	agobiopsia a guida stereotassica o VABB a guida stereotassica
COMPARISON:	agobiopsia ecoguidata o VABB ecoguidata
PURPOSE OF THE TEST:	Diagnosi del cancro della mammella
ANTICIPATED OUTCOMES:	Sensibilità, specificità, eventi avversi, numero di biopsie ripetute, planning errato dell'intervento chirurgico, qualità della vita
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	<p>Le calcificazioni (microcalcificazioni - BIRADS) costituiscono circa un terzo delle lesioni campionate per esami citologici/istologici da pazienti con anomalie rilevate attraverso lo screening. Nei casi di donne con calcificazioni, il campionamento del tessuto può risultare difficile in quanto l'area sospetta potrebbe non essere ben delimitata dall'immagine; le calcificazioni spesso non sono visibili all'ecografia (US) e la modifica istologica associata è di solito non palpabile. Queste considerazioni suggeriscono che la biopsia del tessuto guidata stereotaticamente (NCB) e, in particolare, la VANCB dovrebbero essere la modalità di elezione per il campionamento di queste lesioni. La biopsia guidata dall'ecografia è più facile e meno time-consuming, quindi è importante valutare se la biopsia guidata dall'ecografia o la biopsia guidata stereotaticamente sia preferibile per il campionamento delle calcificazioni.</p> <p>Il carcinoma duttale in situ (DCIS) si presenta tipicamente con calcificazioni e può essere accompagnato da un carcinoma invasivo. La rilevazione dell'invasione nei casi predominantemente di DCIS è importante in quanto può influenzare la scelta del trattamento chirurgico primario, in particolare per quanto riguarda il campionamento del linfonodo sentinella. È, quindi, importante che l'area di calcificazione venga adeguatamente campionata per massimizzare le possibilità di rilevare l'invasione nel campione bioptico. Anche se circa due terzi delle biopsie eseguite per la valutazione delle calcificazioni non mostrano malignità, DCIS o carcinoma invasivo, una percentuale di queste biopsie mostra cambiamenti di natura maligna incerta. In particolare, lesioni come l'atipia epiteliale piatta possono essere accompagnate da DCIS. Allo stesso modo, alcune lesioni intrinsecamente benigne come la radial scar e il papilloma che possono, talvolta, presentarsi come calcificazione possono essere associate a una evoluzione maligna.</p>

Un campionamento adeguato è imperativo per consentire una completa valutazione istologica dell'area anomala e per valutare la necessità di ulteriori indagini, trattamenti o follow-up. Un'altra raccomandazione nelle Linee guida, riguardo al metodo di campionamento in lesioni sospette rilevate dall'imaging, raccomanda di utilizzare la core biopsy invece della FNAC. Tenendo conto di questa raccomandazione, in questo confronto tra la guida dell'ecografia e quella stereotattica, la ricerca della letteratura è stata limitata alla NCB e alla VANCB, escludendo la FNAC.

**CONFLICT OF INTEREST:**

Gestione del conflitto di interesse (CoI): Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

**VALUTAZIONE**

<b>Problem</b> Is the problem a priority?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Calcifications (microcalcifications in previous BIRADS) account for 30-40% of the screen detected lesions with a probability of being malignant of around 13% pending on the type of calcification (1)(Rominger et al., 2012). Calcifications are a typical sign of DCIS, but DCIS might be associated with invasive cancer. Nevertheless, the majority of the lesions that are biopsied because of suspicious calcifications are benign. However, some of these have uncertain malignant potential, like flat epithelial atypia (FEA) or atypical ductal hyperplasia (ADH). Therefore, the clinical consequences are quite variable and depend on the histological diagnosis. It is crucial that the calcifications have been adequately sampled to ensure that women are offered adequate treatment based on the histologically detected lesion that is associated with the calcification. Inadequate sampling of the calcifications could result in false-negative primary biopsies and additionally require further biopsies or surgical interventions.	The GDG selected this question as a priority for ECIBC. As agreement within the GDG could not be reached, voting among the members without CoI resulted in the following: 16 members voted "yes", 1 member voted "probably yes".
<b>Test accuracy</b> How accurate is the test?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very inaccurate</li> <li><input type="radio"/> Inaccurate</li> <li><input type="radio"/> Accurate</li> <li><input checked="" type="radio"/> Very accurate</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		The GDG noted that both tests, compared to the reference standard, are very accurate as both have a sensitivity and specificity above 90%. The reference standard in both comparisons was open biopsy after surgery or follow-up.
<b>Desirable Effects</b> How substantial are the desirable anticipated effects?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> Large</li> </ul>		There is a paucity of studies reporting the use of US guidance for evaluating breast calcifications (microcalcifications in previous BIRADS). This is likely to

- o Varies
- o Don't know

**Part A. Stereotactic-guided needle core biopsy versus reference standard**

Stereotactic-guided needle core biopsy  
 Sensitivity 98 (95 to 99)-pooled  
 Specificity 98 (94 to 99)- pooled

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 34% <sup>a</sup>	pre-test probability of 50% <sup>a</sup>	
<b>True positives</b> (patients with breast cancer)	23 studies 5349 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	not serious	none	333 (323 to 337)	490 (475 to 495)	⊕⊕⊕○ MODERATE
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)								7 (3 to 17)	10 (5 to 25)	
<b>True negatives</b> (patients without breast cancer)	23 studies 5349 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	not serious	none	647 (620 to 653)	490 (470 to 496)	⊕⊕⊕○ MODERATE
<b>False positives</b> (patients incorrectly classified as having breast cancer)								13 (7 to 40)	10 (5 to 30)	

- a. Indirect comparisons. Stereotactic-guided biopsy was compared with a reference standard and accuracy estimates do not represent the effect over ultrasound-guided method.
- b. Median prevalence extracted from Dahabreh 2014.

(Dahabreh II, 2014)

**Part B. Ultrasound-guided needle core biopsy versus reference standard**

Ultrasound-guided needle core biopsy<sup>d</sup>  
 Sensitivity 0.90 to 1.00-range  
 Specificity 1.00 to 1.00-range

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 34% <sup>a</sup>	pre-test probability of 50% <sup>a</sup>	
<b>True positives</b> (patients with breast cancer)	2 studies 135 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	Serious <sup>b</sup>	none	306 to 340	450	⊕⊕○○ LOW
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)								0 to 34	50	
<b>True negatives</b> (patients without breast cancer)	2 studies 135 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	Serious <sup>b</sup>	none	660	500	⊕⊕○○ LOW
<b>False positives</b> (patients incorrectly classified as having breast cancer)								0	0	

- a. Indirect comparisons. Ultrasound-guided needle core biopsy was compared with a reference standard and accuracy estimates do not represent the effect over stereotactic-guided method.
- b. Based on 2 studies with limited sample size and number of events. Percentage of calcifications: Hahn 2011= 100%; Kim 2008= 100%.
- c. Median prevalence extracted from Dahabreh 2014.
- d. Due to scarcity of data, we were unable to perform a meta-analysis for Ultrasound-guided biopsy studies.

(Dahabreh II, 2014)

be due to the limitations of ultrasound in visualising calcifications.

For several years, it has been debated in the literature the potential of US to detect mammary calcifications.

To date, no imaging modality other than x-ray mammography has an accepted role in the detection of mammary calcifications. Despite this, since the implementation and improvement of high-frequency US equipment, the quality of breast US has markedly improved. However, the capability and reliability of this improved US equipment in detecting calcifications has not been adequately studied yet. The GDG noted that with the lower test accuracy estimate,, when using stereotactic-guided biopsy there were 27 more true positives and 27 fewer false negatives per 1000 women with calcifications compared to using ultrasound- guided biopsy (See table labelled part C).

**Part C: Stereotactic-guided needle core biopsy versus ultrasound-guided needle core biopsy**

	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy
Sensitivity	98 (CI 95% = 95 to 99)	Range: 0.90 to 0.99
Specificity	98 (CI 95% = 94 to 99)	Range: 0.99 to 0.99

Outcome	Effect per 1,000 patients tested		Effect per 1,000 patients tested		Test accuracy QoE
	pre-test probability of 34%		pre-test probability of 50%		
	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy	
<b>True positives</b> (patients with breast cancer)	333	High sensitivity: 337 Low sensitivity: 306	490	High sensitivity: 495 Low sensitivity: 450	⊕⊕○○ LOW
	<b>4 fewer to 27 more TP in stereotactic-guided needle core biopsy</b>		<b>40 more to 5 fewer TP in stereotactic-guided needle core biopsy</b>		
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)	7	High sensitivity: 3 Low sensitivity: 34	10	High sensitivity: 5 Low sensitivity: 50	
	<b>4 more to 27 fewer FN in stereotactic-guided needle core biopsy</b>		<b>5 more to 40 fewer FN in stereotactic-guided needle core biopsy</b>		
<b>True negatives</b> (patients without breast cancer)	647	653	490	495	⊕⊕○○ LOW
	<b>6 fewer TN in stereotactic-guided needle core biopsy</b>		<b>5 fewer TN in stereotactic-guided needle core biopsy</b>		
<b>False positives</b> (patients incorrectly classified as having breast cancer)	13	7	10	5	
	<b>6 more FP in stereotactic-guided needle core biopsy</b>		<b>5 more FP in stereotactic-guided needle core biopsy</b>		

**Undesirable Effects**

How substantial are the undesirable anticipated effects?

**GIUDIZI**

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

**RICERCA DELLE PROVE DI EVIDENZA**

**Part A. Stereotactic-guided needle core biopsy versus reference standard**

	Stereotactic-guided needle core biopsy
Sensitivity	98 (95 to 99)-pooled
Specificity	98 (94 to 99)- pooled

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 34% <sup>a</sup>	pre-test probability of 50% <sup>a</sup>	
<b>True positives</b> (patients with breast cancer)	23 studies 5349 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	not serious	none	333 (323 to 337)	490 (475 to 495)	⊕⊕⊕○ MODERATE
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)							7 (3 to 17)	10 (5 to 25)		
<b>True negatives</b> (patients without breast cancer)	23 studies 5349 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	not serious	none	647 (620 to 653)	490 (470 to 496)	⊕⊕⊕○ MODERATE
<b>False positives</b> (patients incorrectly classified as having breast cancer)							13 (7 to 40)	10 (5 to 30)		

a. Indirect comparisons. Stereotactic-guided biopsy was compared with a reference standard and accuracy estimates do not represent the effect over ultrasound-guided method.  
 b. Median prevalence extracted from Dahabreh 2014.

**CONSIDERAZIONI AGGIUNTIVE**

The GDG noted that with the lower test accuracy estimate, when using stereotactic-guided biopsy there were 6 fewer true negatives and 6 more false positives per 1000 women with calcifications compared to using ultrasound-guided biopsy.

As agreement within the GDG for the undesirable effects could not be reached, voting among the members without Col resulted in the following: 1 member voted "moderate", 8 members voted "small" and 8 members voted "trivial". The GDG agrees that the undesirable effects tend to be small.

(Dahabreh JJ, 2014)

**Part B: Ultrasound-guided needle core biopsy versus reference standard**

	Ultrasound-guided needle core biopsy <sup>d</sup>
Sensitivity	0.90 to 1.00-range
Specificity	1.00 to 1.00-range

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 34% <sup>a</sup>	pre-test probability of 50% <sup>a</sup>	
<b>True positives</b> (patients with breast cancer)	2 studies 135 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	Serious <sup>b</sup>	none	306 to 340	450	⊕⊕○○ LOW
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)							0 to 34	50		
<b>True negatives</b> (patients without breast cancer)	2 studies 135 patients	cross-sectional (cohort type accuracy study)	not serious	serious <sup>a</sup>	not serious	Serious <sup>b</sup>	none	660	500	⊕⊕○○ LOW
<b>False positives</b> (patients incorrectly classified as having breast cancer)							0	0		

- a. Indirect comparisons. Ultrasound-guided needle core biopsy was compared with a reference standard and accuracy estimates do not represent the effect over stereotactic-guided method.
- b. Based on 2 studies with limited sample size and number of events. Percentage of calcifications: Hahn 2011= 100%; Kim 2008= 100%.
- c. Median prevalence extracted from Dahabreh 2014.
- d. Due to scarcity of data, we were unable to perform a meta-analysis for Ultrasound-guided biopsy studies.

(Dahabreh JJ, 2014)

**Part C: Stereotactic-guided needle core biopsy versus ultrasound-guided needle core biopsy**

	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy
Sensitivity	98 (CI 95% = 95 to 99)	Range: 0.90 to 0.99
Specificity	98 (CI 95% = 94 to 99)	Range: 0.99 to 0.99

Outcome	Effect per 1,000 patients tested		Effect per 1,000 patients tested		Test accuracy QoE
	pre-test probability of 34%		pre-test probability of 50%		
	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy	Stereotactic-guided needle core biopsy	Ultrasound-guided needle core biopsy	
<b>True positives</b> (patients with breast cancer)	333	High sensitivity: 337 Low sensitivity: 306	490	High sensitivity: 495 Low sensitivity: 450	⊕⊕○○ LOW
	<b>4 fewer to 27 more TP in stereotactic-guided needle core biopsy</b>		<b>40 more to 5 fewer TP in stereotactic-guided needle core biopsy</b>		
<b>False negatives</b> (patients incorrectly classified as not having breast cancer)	7	High sensitivity: 3 Low sensitivity: 34	10	High sensitivity: 5 Low sensitivity: 50	⊕⊕○○ LOW
	<b>4 more to 27 fewer FN in stereotactic-guided needle core biopsy</b>		<b>5 more to 40 fewer FN in stereotactic-guided needle core biopsy</b>		
<b>True negatives</b> (patients without breast cancer)	647	653	490	495	⊕⊕○○ LOW
	<b>6 fewer TN in stereotactic-guided needle core biopsy</b>		<b>5 fewer TN in stereotactic-guided needle core biopsy</b>		
<b>False positives</b> (patients incorrectly classified as having breast cancer)	13	7	10	5	⊕⊕○○ LOW
	<b>6 more FP in stereotactic-guided needle core biopsy</b>		<b>5 more FP in stereotactic-guided needle core biopsy</b>		

## Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>		<p>The GDG agrees that the overall certainty of the evidence is low, due to the quality of the studies for the ultrasound body of evidence, which only has two studies.</p>

## Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>		<p>No studies were included. No evidence was reviewed on the downstream consequences of the false negatives, etc.</p> <p>The GDG noted the uncertainty concerning the cases that are false negatives on biopsy. What happens to a person who is false negative is very variable. It is possible that in multidisciplinary conferences, false negatives are identified due to discordance between imaging and pathology results, and as a result, additional biopsies are recommended. However, other cases might stay undetected for an unknown period of time.</p> <p>Finally, if the lesion remains undetected, the impact will vary depending on the biology of the tumour that has not been diagnosed and on the magnitude of the delay in the diagnosis.</p>

## Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>		<p>No studies were included, but the GDG felt there was very little doubt that the histopathology positive breast cancers would be managed appropriately.</p>



## Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>		<p>No studies were included. However, the GDG discussed the certainty that the women receiving the test would move to the next management step.</p> <p>The GDG noted that false positives are referred to surgery; hence, the GDG felt that it was quite certain that this individual would be managed appropriately. When there is a false negative, the GDG had less certainty on whether the individual would receive appropriate management during the follow-up.</p>

## Certainty of effects

What is the overall certainty of the evidence of effects of the test?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	We have low certainty to perform a comparison between the two assessed techniques, due to one of them having more information (and better quality) than the other.	No studies were included for the overall certainty as, on one hand, there is low certainty of the two assessed techniques in terms of the accuracy of the data and on the other, there are no included studies for the rest of the aspects.

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>	No systematic review was conducted.	The GDG judged that possibly there would be important variability in how women would value the outcomes.

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No systematic review was conducted.</p>	<p>The GDG judged that probably the balance favours stereotactic-guided needle core biopsy over ultrasound-guided needle core biopsy.</p>

## Resources required

How large are the resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><i>Loading...</i> (Hukkinen K, 2008) (Vimpeli SM, 2008)</p>	<p>Regarding ultrasound-guided NCB, differences between Hukkinen (Hukkinen K, 2008) and Vimpeli (Vimpeli SM, 2008) are because Vimpeli (Vimpeli SM, 2008) did not include surgery costs and, therefore the amount of 83€ was lower than the 176€. Regarding the difference between the 83€ for ultrasound-guided NCB and the 246€ for stereotactic-guided NCB, this was due to the equipment costs, which was 3 € for the ultrasound and 152 € for the stereotaxy.</p> <p>The GDG noted that the costs may be higher with US-NCB than those reported in the Vimpeli and Hukkinen studies, because you may have to re-biopsy more frequently.</p>

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p><b>Low certainty</b> due to indirectness. Both studies were conducted in Finland and were 10 years old. Costs and resources used may not be applicable to other European settings.</p>

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	<p>No relevant economic evaluations were identified.</p>	

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No systematic review was conducted.</p>	<p>The GDG reasoned that as the availability of stereotactic-guided NCB is quite low, recommending its use would probably increase inequity regarding its accessibility, therefore probably reducing equity.</p>

## Acceptability

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was conducted.	The GDG judged that the acceptability for key stakeholders would be as follows. <u>For women:</u> US, where women are lying down, may be more comfortable than stereotaxy where there may be more compression and it may be more traumatic for women. Nonetheless, overall the GDG felt that the majority of women would find the intervention acceptable. <u>For radiologists:</u> they may be more comfortable with US-guided procedure and may prefer to perform this over stereotaxy. Panel members were concerned about acceptability. Therefore, as agreement within the GDG for the acceptability could not be reached, voting among the members without CoI resulted in the following: <b>11 members voted "probably yes", one member voted "probably no"; three members voted "varies"; and one member voted "yes".</b>

## Feasibility

Is the intervention feasible to implement?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was conducted.	The GDG agreed the intervention would be feasible.

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLOPMENT
PROBLEM	Yes	The same as original
TEST ACCURACY	Very accurate	The same as original
DESIRABLE EFFECTS	Moderate	The same as original
UNDESIRABLE EFFECTS	Small	The same as original

CRITERI	ORIGINAL	ADOLOPMENT
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Low	The same as original
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	No included studies	The same as original
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	No included studies	The same as original
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	No included studies	The same as original
CERTAINTY OF EFFECTS	No included studies	The same as original
VALUES	Possibly important uncertainty or variability	The same as original
BALANCE OF EFFECTS	Probably favors the intervention	The same as original
RESOURCES REQUIRED	Negligible costs and savings	The same as original
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Low	The same as original
COST EFFECTIVENESS	No included studies	The same as original
EQUITY	Probably reduced	The same as original
ACCEPTABILITY	Probably yes	The same as original
FEASIBILITY	Yes	The same as original

## TIPO DI RACCOMANDAZIONE

Original				
Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Adolopment				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

## CONCLUSIONI

Original

### Recommendation

In individuals presenting with breast calcifications, the ECIBC's Guidelines Development Group recommends the use of stereotactic-guided needle core biopsy over ultrasound-guided needle core biopsy to diagnose the presence of breast cancer (strong recommendation, low certainty evidence).

### Justification

The GDG noted that while stereotactic guidance is favourable, in practice there was low certainty in the evidence reviewed that compared stereotactic to ultrasound guidance. Despite this, the GDG agreed that, when comparing stereotactic-guided NCB with open biopsy, the recommendation was strong and the certainty of this evidence was high. However, when comparing stereotactic guidance to ultrasound guidance, as there were no studies directly comparing both interventions, the overall certainty of the evidence was low, due to the low quality of the evidence for ultrasound guidance compared to open biopsy, as well as the fact that only two studies were found on ultrasound guidance. The GDG agreed to issue a strong recommendation in favour of the use of stereotactic guidance for biopsy evaluation of breast calcification despite the low certainty of the evidence. The radiologist GDG members advised the group that this technique poses less risk for the individual and permits accurate visualisation and targeted biopsy of the calcification. The GDG histopathologists confirmed that their experience indicates that stereotactic-guided biopsy is far superior to ultrasound-guided biopsy in obtaining representative tissue samples of calcification for microscopic evaluation.

Adolopment

### Recommendation

Nelle donne che si presentano con calcificazioni, il pane raccomanda l'uso della core biopsy a guida stereotattica rispetto a quella a guida ecografica per la diagnosi di cancro della mammella (raccomandazione forte, bassa certezza nelle evidenze)

### Justification

## Subgroup considerations

Original

None considered.

Adolopment

La raccomandazione "forte" ha maggiori evidenze laddove non vi siano masse associate.

Se evidenza di lesione focale all'ecografia, si ricorre preferenzialmente all'agobiopsia; se lesione invisibile ad eco, l'evidenza è a favore della VABB a guida stereotassica.

Considerare evidenze per sottogruppi di calcificazioni

## Implementation considerations

Original

1. Training for radiologists who currently biopsy for calcifications using US-NCB.
2. The GDG noted that effective communication strategies are critical so that women can make informed-decisions throughout all phases of the screening process.
3. In settings where stereotactic equipment is not widely available there may be a need to consider how to refer patients to a reference setting where they can have access to stereotactic-guided biopsy.

Adolpment

In Italia la biopsia a guida stereotassica è più spesso associata a VABB. Il rischio di non campionare la lesione è minore con la VABB a prescindere dalla guida utilizzata. E' necessaria formazione per i radiologi che attualmente eseguono biopsie per calcificazioni utilizzando US-NCB.

Il panel italiano condivide l'opinione del panel europeo che le strategie di comunicazione efficaci sono particolarmente importanti affinché le donne possano prendere decisioni informate durante tutte le fasi del processo di screening.

In contesti in cui l'equipaggiamento stereotattico non è ampiamente disponibile, potrebbe essere necessario valutare come indirizzare le pazienti a un contesto di riferimento dove possono avere accesso alla biopsia guidata stereotattica.

## Monitoring and evaluation

Original

Adolpment

Nessuna considerazione

## Research priorities

Original

1. Research was suggested to be done by the GDG on communication strategies for diagnostic tests that are used in different settings, in order to promote informed decision-making by women.

Adolpment

Si suggerisce di fare ricerca sulle strategie di comunicazione dei test diagnostici che sono effettuati in setting differenti, per promuovere il processo decisionale informato.

## REFERENCES SUMMARY

1. Farshid G, Sullivan T, Jones S, Roder D.. Performance indices of needle biopsy procedures for the assessment of screen detected abnormalities in services accredited by BreastScreen Australia. Asian Pac J Cancer Prev; 2014.

## QUESITO 6

### Dovrebbe posizionamento di clip vs nessuna clip dopo agobiopsia (NCB)/ agobiopsia vacuum assisted (VANCB) essere utilizzato per la scelta della terapia chirurgica in pazienti con cancro della mammella

POPULATION:	donne con cancro della mammella con chirurgia programmata, conservativa oppure mastectomia
INTERVENTION:	posizionamento di clip
COMPARISON:	nessuna clip dopo agobiopsia (NCB)/ agobiopsia vacuum assisted (VANCB)
MAIN OUTCOMES:	Overall survival; stato dei margini; ricorrenza locale; eventi avversi come sanguinamento, infezione, ematoma o dolore
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	<p>La marcatura con clip viene effettuata per dimostrare la corretta posizione della biopsia e per guidare il chirurgo durante l'escissione. È utile anche per il follow-up delle lesioni sospette in imaging con istologia benigna. Dopo il posizionamento del clip, viene eseguita una mammografia per vedere la sua relazione con la lesione.</p> <p>Prima dell'intervento chirurgico, questi clip sono di solito individuati tramite marcatura con filo. In caso di spostamento del clip, la lesione stessa potrebbe essere marcata con il filo al posto del clip. Il posizionamento preciso dei clip all'interno o proprio accanto alla lesione aiuta a ridurre la quantità di tessuto che deve essere rimosso chirurgicamente. A volte, anche diversi clip devono essere posizionati sui margini di una lesione per mostrare l'estensione totale o la malattia e per aiutare l'approccio chirurgico. Dopo la rimozione del tessuto, dovrebbe essere effettuata una radiografia del campione per assicurarsi che il clip sia incluso, indicando che il tessuto rimosso include l'area di interesse.</p> <p>Il trattamento moderno del cancro della mammella è adattato alla biologia, alle dimensioni e alle fasi del tumore. In lesioni palpabili, la terapia neoadiuvante viene talvolta utilizzata per ridurre le dimensioni del tumore e aumentare l'operabilità. In alcuni casi, la mastectomia e/o la dissezione ascellare potrebbero essere evitate se alla terapia neoadiuvante si evidenzia una significativa risposta del tumore. Nel cancro alla mammella localmente avanzato di grandi dimensioni, la chemioterapia neoadiuvante può consentire l'operabilità di tumori inizialmente non operabili (Kümmel S, 2014).</p> <p>I tumori possono scomparire completamente all'imaging per la chemioterapia neoadiuvante (risposta radiologica completa), ma a volte rimangono cellule tumorali residue che devono essere rimosse mediante chirurgia. La marcatura con clip in questi casi è importante per definire l'area di tessuto mammario che deve essere rimossa. Può essere posizionata durante la biopsia o in un secondo momento prima dell'inizio della chemioterapia o durante i primi cicli quando il tumore è ancora visibile.</p> <p>Il clip è anche utile, specialmente per campioni di tumori molto grandi o mastectomie, per indirizzare il patologo al sito del tumore per facilitare il campionamento completo del letto tumorale dove il tumore potrebbe non essere visibile macroscopicamente. Se la lesione o l'area patologica è diffusa, a volte viene utilizzato più di un clip per definire l'estensione della malattia o per mostrare in quali aree di una lesione estesa sono state effettuate le biopsie.</p> <p>Gli svantaggi potrebbero essere un posizionamento scorretto del clip, sia attraverso un posizionamento errato che attraverso il movimento del clip nel tessuto (13-20%). In aggiunta, se effettuato in un secondo momento, ci può essere rischio di sanguinamento o infezione anche se in pochi casi.</p>
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (CoI)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
---	--	---	---	---



## CONCLUSIONI

Original

### Recommendation

The ECIBC's Guidelines Development Group suggests using clip-marking after NCB/VANCB for surgical therapy planning in patients with breast cancer lesions (conditional recommendation, very low certainty of the evidence).

### Justification

#### Overall justification

The GDG agreed by consensus to support a conditional recommendation for the intervention.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects were large, including fewer cancers with positive margins and fewer local recurrences with the use of clip-marking after NCB / VANCB for surgical therapy planning.

##### *Undesirable Effects*

The GDG noted differences in the performance of clips from the research evidence. The GDG noted that some women may be concerned about having a clip in the breast. The GDG also notes that the materials used in most clips are known to be safe from their use in other devices.

##### *Certainty of evidence*

The GDG noted that only one study with very low certainty of evidence was reviewed. The GDG had significant concern of risk of allocation bias, as it notes that patients in the intervention group receiving clips may have been healthier or had less advanced disease.

##### *Balance of effects*

The GDG judged that the balance of effects probably favours the intervention.

##### *Resources required*

The GDG judged that the intervention would require moderate costs due to the high costs of the clip, however, the GDG noted that the number of women requiring clips would be small.

##### *Cost effectiveness*

No cost-effectiveness studies were included, however, the GDG noted that cost-effectiveness considerations should include the potential for clips to reduce additional interventions such as additional biopsies or surgeries, which would have significant reductions in costs.

Adolopment

### Recommendation

Il panel suggerisce l'utilizzo del clip-marking dopo NCB/VANCB per il planning chirurgico in pazienti con cancro della mammella (raccomandazione su condizione, certezza molto bassa nelle evidenze)

### Justification

#### Overall justification

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects were large, including fewer cancers with positive margins and fewer local recurrences with the use of clip-marking after NCB / VANCB for surgical therapy planning.

### *Undesirable Effects*

The GDG noted differences in the performance of clips from the research evidence. The GDG noted that some women may be concerned about having a clip in the breast. The GDG also notes that the materials used in most clips are known to be safe from their use in other devices.

### *Certainty of evidence*

The GDG noted that only one study with very low certainty of evidence was reviewed. The GDG had significant concern of risk of allocation bias, as it notes that patients in the intervention group receiving clips may have been healthier or had less advanced disease.

### *Balance of effects*

The GDG judged that the balance of effects probably favours the intervention.

### *Resources required*

The GDG judged that the intervention would require moderate costs due to the high costs of the clip, however, the GDG noted that the number of women requiring clips would be small.

### *Cost effectiveness*

No cost-effectiveness studies were included, however, the GDG noted that cost-effectiveness considerations should include the potential for clips to reduce additional interventions such as additional biopsies or surgeries, which would have significant reductions in costs.

## Subgroup considerations

### Original

Palpable lesions possibly candidate for neoadjuvant therapy and non-palpable lesions: the GDG considered both types of lesion and agreed that the evidence did not support distinguishing these subgroups in this recommendation or in any of the ETD considerations. The GDG noted that lesions that are initially palpable may later become non-palpable following neoadjuvant chemotherapy.

### Adolopment

Lesioni palpabili possibili candidate per la terapia neoadiuvante e lesioni non palpabili: il panel ha considerato entrambi i tipi di lesioni e ha concordato sul fatto che le prove non supportassero la distinzione di questi sottogruppi in questa raccomandazione o in nessuna delle considerazioni nell'ETD. Il panel sottolinea che le lesioni inizialmente palpabili potrebbero diventare non palpabili in seguito alla chemioterapia neoadiuvante.

## Implementation considerations

### Original

1. The GDG noted that effective communication at the time of clip insertion is essential to ensure that women understand the implications on future management.
2. The GDG noted that the timing of clip insertion is critical and whether it is feasible to insert clips during initial biopsies instead of a follow-up procedure may change the harm/benefit ratio because of the additional stress, complications and costs associated with placing the clip in a second time.

### Adolopment

Il panel sottolinea che una comunicazione efficace al momento dell'inserimento del clip è essenziale per garantire che le donne comprendano le implicazioni sulla gestione del caso nel futuro

Il panel sottolinea che il momento dell'inserimento del clip è critico e che la fattibilità di inserire i clip durante le biopsie iniziali invece che al follow-up può cambiare il rapporto tra benefici e danni a causa dello stress, delle complicazioni e dei costi aggiuntivi associati all'inserimento del clip una seconda volta.

## Monitoring and evaluation

### Original

The GDG noted that monitoring for whether clips are inserted in the correct position in relation to a lesion is important. The GDG suggests that further assessments are needed for the appropriateness of clip positioning either by radiology follow-up imaging or pathology. The GDG refers this to the QASDG for consideration.

#### Adolopment

Il panel ha osservato che è importante monitorare se i clip vengono inseriti nella posizione corretta rispetto ad una lesione. Il panel suggerisce che ulteriori valutazioni siano necessarie per verificare l'appropriatezza della posizione dei clip, sia attraverso imaging di follow-up radiologico che tramite anatomia patologica.

## Research priorities

#### Original

1. The GDG suggests the need for more and higher quality evidence on the effectiveness of the intervention improved research with higher quality of evidence from observational studies or where clip-marking is not routinely used considering the use of randomized studies for high quality evidence. The GDG notes that improved evidence on the effectiveness is very important. Some members of the GDG suggested that in the context of clinical equipoise randomized trials would provide higher quality evidence.
2. The GDG suggests further research on the local effects of clips and impacts on the psychological wellbeing for women and whether there is an impact of clips on breast cancer progression or recurrence.
3. The GDG suggests improved cost-effectiveness evidence on the use of clip-marking and comparing the economic impact of clip-marking on the need for additional procedures such as biopsies and surgeries.4. The GDG suggests research on the use of clip-marking for palpable vs non-palpable lesions.

#### Adolopment

1. Il panel segnala la necessità di una maggior quantità e qualità delle evidenze sull'efficacia dell'intervento, migliorando la ricerca con studi osservazionali di maggiore qualità o dove l'uso di clip non è routinario, considerando l'utilizzo di studi randomizzati per ottenere evidenze di alta qualità. Il panel evidenzia che migliorare le evidenze sull'efficacia dell'intervento è molto importante.
2. Il panel suggerisce ulteriori ricerche sugli effetti locali delle clip e sulle conseguenze per il benessere psicologico delle donne, e se le clip hanno un impatto sulla progressione o sulla recidiva del tumore
3. Il panel suggerisce di migliorare le evidenze sull'efficacia costo-beneficio dell'uso di clip, e di confrontare l'impatto economico dell'uso di clip con la necessità di procedure aggiuntive come biopsie e interventi chirurgici.
4. Il panel suggerisce di fare ricerca sull'uso di clip per lesioni palpabili e non palpabili.

## QUESITO 7

### Dovrebbe esami convenzionali per la stadiazione vs nessun esame essere utilizzato per pazienti con cancro alla mammella al primo stadio senza segni suggestivi per metastasi

POPULATION:	Pazienti con cancro alla mammella al primo stadio senza segni suggestivi per metastasi
INTERVENTION:	esami convenzionali per la stadiazione
COMPARISON:	nessun esame
MAIN OUTCOMES:	Detection rate: test combinati (prevalenza); Falsi Positivi: test combinati; Detection rate: Bone Scan; Falsi Positivi: Bone Scan; Detection rate: TC torace; Falsi Positivi: TC torace; Detection rate: CT Pelvica; Falsi Positivi: CT Pelvica; Detection rate: TC addome; Falsi Positivi: TC addome; Detection rate: Rx torace; Falsi Positivi: Rx torace; Detection rate: ecografia; False positive: ecografia
SETTING:	Italia

<b>PERSPECTIVE:</b>	Popolazione (Servizio Sanitario Nazionale)
<b>BACKGROUND:</b>	<p>La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.</p> <p>Per i casi di tumore della mammella diagnosticati nel 2005-2009 la sopravvivenza netta standardizzata a 5 anni è dell'87%. Anche se in crescita, la prognosi a 5 anni permane significativamente inferiore al Sud (85%), mentre è sovrapponibile nelle altre aree (E&amp;P 2017, I TUMORI IN ITALIA RAPPORTO AIRTUM 2016 SOPRAVVIVENZA).</p>
<b>CONFLICT OF INTEREST:</b>	<u>Gestione del conflitto di interesse (CoI)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## VALUTAZIONE

<b>Problem</b> Is the problem a priority?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The detection of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer and, in some cases, to start treatments that are specific for metastases</p> <p>Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, they are also associated with some disadvantages like limited specificity, leading to false positive with consequent psychological stress for the women, unnecessary ascertainment and, when ascertainment is not possible leading to wrong treatment planning; furthermore some imaging techniques have procedure related consequences, in particular radiation (depending on the used technique) and high costs.</p>	The GDG prioritised this question for the ECIBC.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze locali di contesto per l'Italia	

## Desirable Effects

How substantial are the desirable anticipated effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE																																
<ul style="list-style-type: none"> <li>● Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>○ Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<table border="1" data-bbox="533 357 1525 1061"> <thead> <tr> <th>Outcomes</th> <th>Impact</th> <th>№ of participants (studies)</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Detection rate: Combined tests (prevalence)</td> <td>Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958</td> <td>(5 RCTs)<sup>1,2,3,4,5</sup></td> <td>⊕⊕○○ LOW<sup>a,b,c,d</sup></td> </tr> <tr> <td>Detection rate: Bone Scan</td> <td>Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397</td> <td>(5 RCTs)<sup>1,2,4,6,7</sup></td> <td>⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td>Detection rate: TC chest</td> <td>Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485</td> <td>(2 RCTs)<sup>1,8</sup></td> <td>⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td>Detection rate: CT Pelvic</td> <td>Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32</td> <td>(1 RCT)<sup>1</sup></td> <td>⊕○○○ VERY LOW<sup>a,b,d,e,f</sup></td> </tr> <tr> <td>Detection rate: TC abdominal</td> <td>Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43</td> <td>(1 RCT)<sup>1</sup></td> <td>⊕○○○ VERY LOW<sup>a,b,d,e,f</sup></td> </tr> <tr> <td>Detection rate: Chest X-Ray</td> <td>Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049</td> <td>(3 RCTs)<sup>1,2,5</sup></td> <td>⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td>Detection rate: US</td> <td>Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407</td> <td>(3 RCTs)<sup>1,2,4</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,b,e</sup></td> </tr> </tbody> </table> <p data-bbox="577 1102 1525 1410">                 2. Dillman RO, Chico S.. Radiologic tests after a new diagnosis of breast cancer.. Eff Clin Pract.; 2000.                  3. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andretta C, Di Terlizzi S, Piga A.. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications.. Ann Oncol.; 2005.                  4. Ravaioli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.                  5. Kasem AR, Desai A, Daniell S, Sinha P.. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer. Breast J. ; 2006.                  6. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.             </p>	Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>	Detection rate: Bone Scan	Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397	(5 RCTs) <sup>1,2,4,6,7</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: TC chest	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485	(2 RCTs) <sup>1,8</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: CT Pelvic	Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>	Detection rate: TC abdominal	Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>	Detection rate: Chest X-Ray	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049	(3 RCTs) <sup>1,2,5</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: US	Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407	(3 RCTs) <sup>1,2,4</sup>	⊕⊕⊕○ MODERATE <sup>a,b,e</sup>	<p data-bbox="1541 252 2029 328">Sensitivity analysis without Puglisi (2005): *Pooled detection rate: 1 per 1,000 examinations (95% CI: 0 - 8); n/N = 3/1722 (4 studies)</p> <p data-bbox="1541 384 2029 719">In one study including 411 clinical stage II breast cancer patients (Bychkovsky BL, 2006) evaluated by conventional imaging, the percentage of distant metastases did not differ by BC subtype: among ER/PR-positive and HER2-negative patients was 2.2% (95% CI, 0.5%–6.4%), for HER2+ patients was 1.9% (95% CI, 0%–9.9%), and in TNBC patients was 2.1% (95% CI, 0.1%–11.1%). Another study in 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (Groheux D, 2012), reported that the rates of distant metastases did not differ between TNBC (16%), HER2- positive (26%), and ER-positive (22%) breast cancers subtypes (p = 0.42).</p> <p data-bbox="1541 775 2029 879">It must be kept in mind that these two studies do not include clinical stage I breast cancer patients, and the evidence is indirect. The GDG judged by consensus that the desirable effects were trivial.</p>
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)																															
Detection rate: Combined tests (prevalence)	Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>																															
Detection rate: Bone Scan	Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397	(5 RCTs) <sup>1,2,4,6,7</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: TC chest	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485	(2 RCTs) <sup>1,8</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: CT Pelvic	Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>																															
Detection rate: TC abdominal	Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>																															
Detection rate: Chest X-Ray	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049	(3 RCTs) <sup>1,2,5</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: US	Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407	(3 RCTs) <sup>1,2,4</sup>	⊕⊕⊕○ MODERATE <sup>a,b,e</sup>																															

7. Lee JE, Park SS, Han W, Kim SW, Shin HJ, Choe KJ, Oh SK, Youn YK, Noh DY, Kim SW.. The clinical use of staging bone scan in patients with breast carcinoma: reevaluation by the 2003 American Joint Committee on Cancer staging system.. Cancer. ; 2005.
  8. Koizumi M, Yoshimoto M, Kasumi F, Ogata E.. What do breast cancer patients benefit from staging bone scintigraphy?. Jpn J Clin Oncol.; 2001.
  9. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition
  - b. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggests that only a subpopulation of these cases entered in the study and that they could be those with higher suspicion of having distal metastases.
  - c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimate the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.
  - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
  - f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False Positive: Combined tests (prevalence)	Pooled false positive: 49 per 1,000 examinations (95% CI: 4 - 131); n/N = 29/1,220	(3 RCTs) <sup>1,2,3</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>
False positive: Bone Scan	False positive: 164 per 1,000 examinations (95% CI: 91.6 - 276.1); n/N = 10/61	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,b,e,f</sup>
False positive: TC chest	False positive: 134 per 1,000 examinations (95% CI: 106 - 169); n/N = 60/448	(1 RCT) <sup>4</sup>	⊕⊕○○ LOW <sup>a,b,e,f</sup>
False positive: CT Pelvic - not reported		-	-

False positive: TC abdominal - not reported		-	-
False positive: Chest X-Ray - not reported		-	-
False positive: US	False positive: 16 per 1,000 examinations (95% CI: 3 - 87); n/N = 1/61	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,b,e,g</sup>

1. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  2. Kasem AR, Desai A, Daniell S, Sinha P. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer. Breast J. ; 2006.
  3. Ravaoli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.
  4. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma. Breast Cancer Res Treat.; 2011.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition
  - b. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggest that only a subpopulation of these cases entered in the study and that they could be those with higher suspicious of having distal metastases.
  - c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.
  - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
  - f. Judgement about inconsistency was considered serious given that the reported detected rate was inconsistent with other studies performed in the same stage and applying similar procedures to identify distant metastases.
  - g. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE																																
<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>● Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Original</p> <table border="1" data-bbox="533 403 1525 1109"> <thead> <tr> <th data-bbox="533 403 779 499">Outcomes</th> <th data-bbox="779 403 1173 499">Impact</th> <th data-bbox="1173 403 1323 499">N<sub>e</sub> of participants (studies)</th> <th data-bbox="1323 403 1525 499">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td data-bbox="533 499 779 595">Detection rate: Combined tests (prevalence)</td> <td data-bbox="779 499 1173 595">Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958</td> <td data-bbox="1173 499 1323 595">(5 RCTs)<sup>1,2,3,4,5</sup></td> <td data-bbox="1323 499 1525 595">⊕⊕○○ LOW<sup>a,b,c,d</sup></td> </tr> <tr> <td data-bbox="533 595 779 691">Detection rate: Bone Scan</td> <td data-bbox="779 595 1173 691">Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397</td> <td data-bbox="1173 595 1323 691">(5 RCTs)<sup>1,2,4,6,7</sup></td> <td data-bbox="1323 595 1525 691">⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td data-bbox="533 691 779 770">Detection rate: TC chest</td> <td data-bbox="779 691 1173 770">Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485</td> <td data-bbox="1173 691 1323 770">(2 RCTs)<sup>1,8</sup></td> <td data-bbox="1323 691 1525 770">⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td data-bbox="533 770 779 850">Detection rate: CT Pelvic</td> <td data-bbox="779 770 1173 850">Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32</td> <td data-bbox="1173 770 1323 850">(1 RCT)<sup>1</sup></td> <td data-bbox="1323 770 1525 850">⊕○○○ VERY LOW<sup>a,b,d,e,f</sup></td> </tr> <tr> <td data-bbox="533 850 779 930">Detection rate: TC abdominal</td> <td data-bbox="779 850 1173 930">Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43</td> <td data-bbox="1173 850 1323 930">(1 RCT)<sup>1</sup></td> <td data-bbox="1323 850 1525 930">⊕○○○ VERY LOW<sup>a,b,d,e,f</sup></td> </tr> <tr> <td data-bbox="533 930 779 1026">Detection rate: Chest X-Ray</td> <td data-bbox="779 930 1173 1026">Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049</td> <td data-bbox="1173 930 1323 1026">(3 RCTs)<sup>1,2,5</sup></td> <td data-bbox="1323 930 1525 1026">⊕⊕○○ LOW<sup>a,b,d,e</sup></td> </tr> <tr> <td data-bbox="533 1026 779 1106">Detection rate: US</td> <td data-bbox="779 1026 1173 1106">Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407</td> <td data-bbox="1173 1026 1323 1106">(3 RCTs)<sup>1,2,4</sup></td> <td data-bbox="1323 1026 1525 1106">⊕⊕⊕○ MODERATE<sup>a,b,e</sup></td> </tr> </tbody> </table> <ol style="list-style-type: none"> <li>1. Dillman RO, Chico S. Radiologic tests after a new diagnosis of breast cancer. Eff Clin Pract.; 2000.</li> <li>2. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andretta C, Di Terlizzi S, Piga A.. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol.; 2005.</li> <li>3. Ravaioli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice? Ann Oncol; 1998.</li> <li>4. Kasem AR, Desai A, Daniell S, Sinha P.. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer. Breast J.; 2006.</li> </ol>	Outcomes	Impact	N <sub>e</sub> of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>	Detection rate: Bone Scan	Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397	(5 RCTs) <sup>1,2,4,6,7</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: TC chest	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485	(2 RCTs) <sup>1,8</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: CT Pelvic	Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>	Detection rate: TC abdominal	Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>	Detection rate: Chest X-Ray	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049	(3 RCTs) <sup>1,2,5</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>	Detection rate: US	Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407	(3 RCTs) <sup>1,2,4</sup>	⊕⊕⊕○ MODERATE <sup>a,b,e</sup>	<p>The GDG judged by consensus that the undesirable effects were small.</p>
Outcomes	Impact	N <sub>e</sub> of participants (studies)	Certainty of the evidence (GRADE)																															
Detection rate: Combined tests (prevalence)	Pooled detection rate: 8 per 1,000 examinations (95% CI: 0 - 30); n/N = 15/1,958	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>																															
Detection rate: Bone Scan	Pooled detection rate: 5 per 1,000 examinations (95% CI 0 - 21) n/N = 17/2,397	(5 RCTs) <sup>1,2,4,6,7</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: TC chest	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 5) n/N = 2/485	(2 RCTs) <sup>1,8</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: CT Pelvic	Detection rate: 31 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/32	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>																															
Detection rate: TC abdominal	Detection rate: 23 per 1,000 examinations (95% CI: 7.3 - 92.1); n/N = 1/43	(1 RCT) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,d,e,f</sup>																															
Detection rate: Chest X-Ray	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 2); n/N = 0/1,049	(3 RCTs) <sup>1,2,5</sup>	⊕⊕○○ LOW <sup>a,b,d,e</sup>																															
Detection rate: US	Pooled detection rate: 0 per 1000 examinations (95% CI: 0 - 11); n/N = 1/407	(3 RCTs) <sup>1,2,4</sup>	⊕⊕⊕○ MODERATE <sup>a,b,e</sup>																															



5. Barret T, Bowden DJ,Greenberg DC,Brown CH,Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  6. Lee JE, Park SS,Han W,Kim SW,Shin HJ,Choe KJ,Oh SK,Youn YK,Noh DY,Kim SW.. The clinical use of staging bone scan in patients with breast carcinoma: reevaluation by the 2003 American Joint Committee on Cancer staging system Cancer, 2005.
  7. Koizumi M, Yoshimoto M,Kasumi F,Ogata E.. What do breast cancer patients benefit from staging bone scintigraphy? Jpn J Clin Oncol.; 2001.
  8. Kim H, Han W,Moon HG,Min J,Ahn SK,Kim TY,Im SA,Oh DY,Han SW,Chie EK,Ha SW,Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma. Breast Cancer Res Treat.; 2011.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.
  - b. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggest that only a subpopulation of these cases entered in the study and that they could be those with higher suspicious of having distal metastases.
  - c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.
  - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
  - f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Outcomes	Impact	N <sub>o</sub> of participants (studies)	Certainty of the evidence (GRADE)
False Positive: Combined tests (prevalence)	Pooled false positive: 49 per 1,000 examinations (95% CI: 4 - 131); n/N = 29/1,220	(3 RCTs) <sup>1,2,3</sup>	⊕⊕○○ LOW <sup>a,b,c,d</sup>
False positive: Bone Scan	False positive: 164 per 1,000 examinations (95% CI: 91.6 - 276.1); n/N = 10/61	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,b,e,f</sup>
False positive: TC chest	False positive: 134 per 1,000 examinations (95% CI: 106 - 169); n/N = 60/448	(1 RCT) <sup>4</sup>	⊕⊕○○ LOW <sup>a,b,e,f</sup>
False positive: CT Pelvic - not reported		-	-

False positive: TC abdominal - not reported		-	-
False positive: Chest X-Ray - not reported		-	-
False positive: US	False positive: 16 per 1,000 examinations (95% CI: 3 - 87); n/N = 1/61	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,b,e,g</sup>

1. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  2. Kasem AR, Desai A, Daniell S, Sinha P.. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer. Breast J; 2006.
  3. Ravaoli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice? Ann Oncol; 1998.
  4. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma. Breast Cancer Res Treat.; 2011.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition
  - b. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggest that only a subpopulation of these cases entered in the study and that they could be those with higher suspicious of having distal metastases.
  - c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.
  - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
  - f. Judgement about inconsistency was considered serious given that the reported detected rate was inconsistent with other studies performed in the same stage and applying similar procedures to identify distant metastases.
  - g. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Adolopment

<ul style="list-style-type: none"> <li><input type="radio"/> Large</li> <li><input type="radio"/> Moderate</li> <li><input checked="" type="radio"/> Small</li> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	
--	---	--

## Certainty of evidence

What is the overall certainty of the evidence of effects?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>		The GDG judged by consensus that the certainty of the evidence was low.
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	Secondo il Panel, l'incertezza è soprattutto relativa all'impatto sulla prognosi nell'identificare le metastasi qualora identificate

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>		The GDG judged by consensus that there was possibly important uncertainty or variability in how much women value the main outcomes.

	Adolopment	
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>● Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> <li>○ No known undesirable outcomes</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	
<h3>Balance of effects</h3> <p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p>		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<ul style="list-style-type: none"> <li>● Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>The GDG notes the low certainty of the evidence, notably for the detection rate with conventional staging exams.</p> <p>The GDG also notes the very high 5-year survival for patients with stage I breast cancer.</p> <p>As agreement could not be reached by consensus, voting was conducted among members without COI:  *15 members voted for 'favours the comparison',  *7 members voted for 'probably favors the intervention'.</p>
	Adolopment	
<ul style="list-style-type: none"> <li>● Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	
		Il Panel ritiene che la maggior parte del danno sia legato ai falsi positivi, in confronto ai benefici (pressochè nulli o non valutabili. Questo nonostante l'entità del danno sia piccola considerandola in termini di valore assoluto. Pertanto, si ritiene di favorire il comparatore vs l'intervento.
<h3>Resources required</h3> <p>How large are the resource requirements (costs)?</p>		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	

<ul style="list-style-type: none"> <li>● Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>Direct evidence: Mean cost and utilization</b></p> <p>One Italian study (DePlacido 2017) determined the relative costs of staging and follow-up tests in a population of breast cancer patients in a Southern Italian region. The number and type of tests per patient were recorded 3 months before and 12 months after the date diagnosis of nonmetastatic breast cancer from 2001 to 2010.</p> <table border="1" data-bbox="551 384 1509 772"> <thead> <tr> <th rowspan="2">Type of tests</th> <th colspan="3">Estimated annual variation (2001-2010)</th> </tr> <tr> <th>Mean cost<sup>1</sup> of imaging tests per patient (Euros)</th> <th>Imaging utilization, % (95% CI)</th> <th>Imaging-related costs, % (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Chest radiograph, abdominal ultrasound, bone scan, and mammograms</td> <td>Remain constant at 250 €</td> <td>Increase 0.1% (-0.1–0.3)</td> <td>Decrease 0.1% (-0.9 to 0.6)</td> </tr> <tr> <td>CT, PET, and MRI</td> <td>Increased from 350 € in 2001 to 800 € in 2010</td> <td>Increase 15.7% (14.2–17.2)</td> <td>Increase 19.4% (15.9–23.0)</td> </tr> </tbody> </table> <p><sup>1</sup>Prices were reported in 2011 Euros value.</p>	Type of tests	Estimated annual variation (2001-2010)			Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)	Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1–0.3)	Decrease 0.1% (-0.9 to 0.6)	CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2–17.2)	Increase 19.4% (15.9–23.0)	<p><b>Indirect evidence:</b></p> <p>One study from Canada and two studies from the USA reported costs of imaging tests. The Canadian study reported that patients with stage II incurred higher imaging costs than those with stage I: CAD 535 per capita compared with CAD 204 per capita (2015 Canadian dollars) (Thavorn2016). The USA studies reported that the unitary cost per chest x-rays was USD 96.9, abdominal ultrasound USD 285, CT chest with contrast USD 239 to USD 510, CT abdominal-pelvis with contrast USD 305 to USD 696, body bone scan USD 658 to USD 853.8 (2013-2014 US dollars) (Louie2015, Pellet2016).</p> <p>The GDG notes that due to the lower detection rate for stage I breast cancer the costs per patient with metastasis detected are assumed to be greater than USD 100,000 per case detected.</p> <p>The GDG agreed by consensus that the costs are large.</p>
Type of tests	Estimated annual variation (2001-2010)																
	Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)														
Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1–0.3)	Decrease 0.1% (-0.9 to 0.6)														
CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2–17.2)	Increase 19.4% (15.9–23.0)														
	Adolopment																
<ul style="list-style-type: none"> <li>● Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Non sono state considerate evidenze locali di contesto per l'Italia</p>																

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>Low certainty of the evidence due to indirectness, and imprecision. Costs reported in the study may not be representative of other European settings since it was performed only in Campania, Italy. Also, there is imprecision in the results since the cost of each test was not reported. In fact, only the mean cost of imaging tests per patient (including chest radiograph, abdominal ultrasound, bone scan, and mammograms) were reported.</p>	<p>The cost requirement evidence was based on a single study. The detection rate that was used in the cost study was 3/1000 for the AJCC 6th edition and 12/1000 according to the AJCC 5th edition. The GDG judged that the certainty of evidence of required resources was low.</p>
	Adolopment	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>Non sono state considerate evidenze locali di contesto per l'Italia</p>	

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No relevant economic evaluations were identified	
---	--	--

Adolopment
------------

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	
---	---	--

<h2 style="margin: 0;">Equity</h2> <p style="margin: 0; font-size: small;">What would be the impact on health equity?</p>
---

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
---------	---------------------------------	---------------------------

Original
----------

<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>● Varies</li> <li>○ Don't know</li> </ul>		<p>The GDG notes that when the burden of tests is increased for patients with staging exams, there may be increased costs to patients depending on health care coverage of diagnostic tests for patients.</p> <p>If the wait time is long for publicly funded imaging in a particular setting, patients may opt to pay out of pocket for accelerated staging exams, therefore reducing health equity. The GDG judged by consensus that the impact on health equity would vary.</p>
--	--	--

Adolopment
------------

<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	<p>Aumentare gli esami preoperatori può aumentare le disuguaglianze per l'impatto sui tempi di attesa dell'intervento, a fronte di un beneficio minimo (se esistente). Potrebbe generare una fuga verso il privato per le pazienti più abbienti o culturalmente favorite. I dati più recenti relativi ai tempi di attesa dello screening mammografico si riferiscono al 2019. È opportuno premettere che non tutte le Regioni</p>
--	---	---

conferiscono dati completi. Ad ogni modo in tutto il paese il 65% delle donne ha ricevuto la risposta negativa entro 21 giorni dalla effettuazione della mammografia, il 59% delle donne indirizzate a richiamo per approfondimento lo ha effettuato entro 28 giorni dalla esecuzione della mammografia, mentre solo il 32% delle donne con indicazioni a trattamento lo ha effettuato entro 60 giorni dalla esecuzione della mammografia.

**Acceptability**

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input checked="" type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		<p>The GDG notes that the population of stage I patients is much larger, and therefore the costs will be much larger, policy makers will therefore not likely find the intervention acceptable.</p> <p>The GDG considered that some women may strongly desire staging exams, while other women may be distressed by the staging exams.</p> <p>The GDG judged by consensus that the acceptability varied among women and other key stakeholders.</p>
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input checked="" type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	<p>Aggiungere test alla fase pre-operatoria può allungare i tempi di attesa per la chirurgia rendendo l'intervento proposto meno accettabile</p> <p>I dati più recenti relativi ai tempi di attesa dello screening mammografico si riferiscono al 2019. E' opportuno premettere che non tutte le Regioni conferiscono dati completi. Ad ogni modo in tutto il paese il 65% delle donne ha ricevuto la risposta negativa entro 21 giorni dalla effettuazione della mammografia, il 59% delle donne indirizzate a richiamo per approfondimento lo ha effettuato entro 28 giorni dalla esecuzione della mammografia, mentre solo il 32% delle donne con indicazioni a trattamento lo ha effettuato entro 60 giorni dalla esecuzione della mammografia.</p>



Feasibility		
Is the intervention feasible to implement?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input checked="" type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		<p>The GDG was not aware of any settings where staging exams using imaging for clinical stage I is routinely performed in current practice.</p> <p>As consensus was not reached, voting was conducted among GDG members without COI:</p> <p>*11 members voted 'probably no' 6 'varies'</p> <p>*1 member voted 'probably yes'.</p> <p>*One member did not register a vote.</p>
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input checked="" type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	Non sono state considerate evidenze locali di contesto per l'Italia	I dati più recenti relativi ai tempi di attesa dello screening mammografico si riferiscono al 2019. E' opportuno premettere che non tutte le Regioni conferiscono dati completi. Ad ogni modo in tutto il paese il 65% delle donne ha ricevuto la risposta negativa entro 21 giorni dalla effettuazione della mammografia, il 59% delle donne indirizzate a richiamo per approfondimento lo ha effettuato entro 28 giorni dalla esecuzione della mammografia, mentre solo il 32% delle donne con indicazioni a trattamento lo ha effettuato entro 60 giorni dalla esecuzione della mammografia.

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLOPMENT
PROBLEM	Yes	Yes
DESIRABLE EFFECTS	Trivial	The same as original
UNDESIRABLE EFFECTS	Small	Small
CERTAINTY OF EVIDENCE	Low	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Favors the comparison	Favors the comparison
RESOURCES REQUIRED	Large costs	Large costs

CRITERI	ORIGINAL	ADOLOPMENT
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Low	Low
COST EFFECTIVENESS	No included studies	No included studies
EQUITY	Varies	Probably reduced
ACCEPTABILITY	Varies	Varies
FEASIBILITY	Probably no	Probably no

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention	<b>Conditional recommendation against the intervention</b> ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
--	---	---	--	---

## CONCLUSIONI

### Recommendation

The ECIBC's Guidelines Development Group suggests against using a staging exam with imaging in women with clinical stage I breast cancer (conditional recommendation, low certainty of the evidence).  
**Il panel suggerisce di non utilizzare esami di stadiazione con imaging nelle donne con cancro della mammella in stadio I (raccomandazione su condizione, bassa certezza delle evidenze)**

### Justification

#### Overall justification

As consensus was not reached, voting was conducted among members without COI: 15 members voted in favour of 'strong recommendation against the intervention', 7 members voted in favour of 'conditional recommendation against the intervention'. To make a strong recommendation, the GDG voting rules require a 80% majority in support. Therefore, a conditional recommendation against the intervention was made.

#### Detailed justification

##### Desirable Effects

The desirable effects of the intervention were judged to be trivial. The pooled combined detection rate of metastases (from 6 RCTs) was 6.33 and the 95% confidence interval was 0-24.8 per 1000 women with clinical stage I breast cancer that undergo conventional staging exams.

##### Undesirable Effects

The undesirable effects of the intervention were judged to be small. The pooled false positive rate was 32.4 per 1000 women with clinical stage I breast cancer who undergo staging exams.

##### Balance of effects

The balance of effects was judged to favour the comparison.

##### Resources required

The resources required for the intervention were judged to be large costs. The costs of conventional staging exams for women with stage I cancer was assumed to be greater than \$100,000 per metastasis detected, inferring from evidence on staging exams for women with clinical stage II cancer.

### Subgroup considerations

Original

The GDG noted that women with clinical stage I breast cancer receiving neo-adjuvant chemotherapy may be considered for conventional staging exams using imaging.

Adolopment

Il panel ritiene che le donne con cancro al seno al primo stadio e che ricevono la chemioterapia neoadiuvante possono essere valutate attraverso gli esami di staging convenzionali

## Implementation considerations

Original

1. The GDG considered the definition of stage groups according to the American Joint Commission on Cancer TNM Anatomic Stage Groups (8th ed.) listed in the ECIBC glossary.
2. The GDG notes that there is still uncertainty with the evidence of detection rate using conventional staging exams with imaging.
3. The GDG notes that psychological support may be indicated to assist with follow-up of clinical stage I breast cancers in place of staging exams using imaging for reassurance of women who are very distressed about the potential for metastases.

Adolopment

1. Per lo staging va utilizzato il TNM 8a edizione
2. Vi è ancora incertezza sul detection rate utilizzando le tecniche di imaging convenzionale
3. Può essere indicato un supporto psicologico per supportare le donne allo stadio I nel follow-up a scopo di assicurazione rispetto alla paura di metastasi

## Monitoring and evaluation

Original

1. The GDG suggests monitoring and evaluation efforts to improve compliance with this suggestion to not conduct staging exams using imaging for clinical stage I breast cancers.
2. The GDG suggests assessment by the QASDG for recommendations and implementation of monitoring and evaluation.

Adolopment

Si suggerisce monitoraggio e valutazione per aumentare la compliance alla raccomandazione

## Research priorities

Original

1. The GDG suggests further research to provide higher quality evidence on the detection rate with staging exams using imaging in clinical stage I breast cancers.
2. The GDG suggests further research on clinical stage I breast cancers that are diagnosed and ultimately metastasise to determine causes, and whether the use of staging exams will impact outcomes.
3. The GDG suggests further research to assess the impact of staging exams using imaging for clinical stage I breast cancers with different higher risk histology groups.
4. The GDG suggests further research to assess possible subgroups within clinical stage I breast cancers and varying need for staging exams using imaging.
5. The GDG suggests research on non-ionizing and low-radiation dose alternatives for staging exams using imaging.

Adolopment

1. Si suggerisce ulteriore ricerca per fornire evidenze di maggiore qualità sul detection rate con esami di stadiazione di imaging
2. Si suggerisce ulteriore ricerca sui cancri allo stadio I che metastatizzano per determinarne le cause e se l'uso di esami di stadiazione hanno un impatto sugli outcome
3. Si suggerisce ulteriore ricerca sull'impatto degli esami di stadiazione con imaging sui cancri di stadio uno con diversi tipi di rischio istologico aumentato
4. Si suggerisce ulteriore ricerca rispetto all'individuazione di sottogruppi di cancri di stadio I con necessità di stadiazione differenziate
5. Si suggerisce ulteriore ricerca su alternative agli esami di imaging che non comportino l'esposizione a radiazioni ionizzanti o con radiazioni a bassa dose

## QUESITO 8

### Dovrebbe Esami di stadiazione con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio I senza sintomi suggestivi di metastasi

POPULATION:	Pazienti con cancro della mammella allo stadio I senza sintomi suggestivi per metastasi
INTERVENTION:	Esami di stadiazione con 18F-FDG PET-CT
COMPARISON:	esami di stadiazione senza PET
MAIN OUTCOMES:	Detection rate; Falsi positivi;
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
CONFLICT OF INTEREST:	Gestione del conflitto di interesse (CoI): Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Original				
Strong recommendation against the intervention ●	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Adolopment				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

## CONCLUSIONI

Original

## Recommendation

For patients with clinical stage I breast cancer without symptoms suggestive of metastases , the ECIBC's Guidelines Development Group (GDG) recommends against using positron emission tomography-computed tomography (PET-CT) staging exams (strong recommendation, very low certainty of the evidence).

## Justification

### Overall Justification

The GDG agreed by consensus to recommend strongly against this intervention.

Adolopment

## Recommendation

**Per le pazienti con cancro della mammella allo stadio I senza sintomi suggestivi per metastasi, il panel raccomanda di non utilizzare la PET-CT per la stadiazione (raccomandazione forte, certezza nelle evidenze molto bassa)**

## Justification

## Subgroup considerations

Original

For triple negative tumours and HER2 positive evidence suggests that there is no additional benefit because of no increased risks from metastases.

Adolopment

Per i tumori triplo negativi e HER2 positivi le evidenze suggeriscono che non ci sia un beneficio aggiuntivo perché non c'è rischio aumentato di metastasi

## Implementation considerations

Original

None were considered by the GDG.

Adolopment

Nessuna considerazione del panel

## Monitoring and evaluation

Original

None were considered by the GDG.

Adolopment

Nessuna considerazione del panel

## Research priorities

Original

The GDG suggests research to clarify the clinical significance of true positives (for all stages).

Adolopment

Nessuna considerazione del panel

## QUESITO 9

**Dovrebbe esami convenzionali per la stadiazione vs nessun esame per la stadiazione essere utilizzato per pazienti con cancro alla mammella al secondo stadio senza segni suggestivi per metastasi**

POPULATION:	pazienti con cancro alla mammella al secondo stadio senza segni suggestivi per metastasi
INTERVENTION:	esami convenzionali per la stadiazione
COMPARISON:	nessun esame per la stadiazione
MAIN OUTCOMES:	Detection rate: test combinati (prevalenza); Falsi Positivi: test combinati; Detection rate: Bone Scan; Falsi Positivi: Bone Scan; Detection rate: TC torace; Falsi Positivi: TC torace; Detection rate: CT Pelvica ; Falsi Positivi: CT Pelvica; Detection rate: TC addome; Falsi Positivi: TC addome; Detection rate: Rx torace; Falsi Positivi: Rx torace; Detection rate: ecografia; False positive: ecografia
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (CoI)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention <input type="radio"/>	<b>Conditional recommendation against the intervention</b> <input checked="" type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
---	--	---	--	---

## CONCLUSIONI

Original



## Recommendation

The ECIBC's Guidelines Development Group suggests against using a staging exams with imaging in women with clinical stage IIa and IIb breast cancer (conditional recommendation, low certainty of the evidence).

## Justification

### Overall justification

The GDG reached consensus suggesting against the intervention of staging exams using imaging for women presenting with clinical stage II breast cancer.

### Detailed justification

#### *Desirable Effects*

The GDG judged that the desirable effects were small.

#### *Undesirable Effects*

The GDG judged that the undesirable effects varied. For clinical stage IIa breast cancer the undesirable effects due to false positives were small. For clinical stage IIb breast cancer the undesirable effects due to false positives were moderate.

#### *Values*

The GDG did not conduct a systematic review for values and preferences regarding diagnostic exams. The GDG notes that due to the variety of diagnostic and treatment pathways the values and preferences for each may be very heterogeneous.

#### *Resources required*

The GDG judged that the resources required for clinical stage IIa breast cancer were large and for IIb breast cancer were moderate.

#### *Feasibility*

The feasibility may vary by setting. If there is a screening program in place there will likely be more clinical stage I breast cancer presentations, and if there is no screening program there will likely be more symptomatic clinical stage II breast cancer presentations. This will affect the volume of staging exams using imaging and therefore the feasibility.

Adolpment

## Recommendation

Il panel suggerisce di non utilizzare esami di stadiazione con imaging nelle donne con cancro della mammella in stadio IIa e IIb (raccomandazione su condizione, bassa certezza delle evidenze)

## Justification

### Overall justification

### Detailed justification

#### *Desirable Effects*

The GDG judged that the desirable effects were small.

#### *Undesirable Effects*

The GDG judged that the undesirable effects varied. For clinical stage IIa breast cancer the undesirable effects due to false positives were small. For clinical stage IIb breast cancer the undesirable effects due to false positives were moderate.

#### *Values*

The GDG did not conduct a systematic review for values and preferences regarding diagnostic exams. The GDG notes that due to the variety of diagnostic and treatment pathways the values and preferences for each may be very heterogeneous.

#### *Resources required*

The GDG judged that the resources required for clinical stage IIa breast cancer were large and for IIb breast cancer were moderate.

#### *Feasibility*

The feasibility may vary by setting. If there is a screening program in place there will likely be more clinical stage I breast cancer presentations, and if there is no screening program there will likely be more symptomatic clinical stage II breast cancer presentations. This will affect the volume of staging exams using imaging and therefore the feasibility.

## Subgroup considerations

Original

1. For clinical stage II breast cancers, the GDG notes that there is no evidence of an increased detection rate according to hormone receptor and HER2 status, although these results might influence the decision to conduct further imaging because of the possible impact on treatment strategies.
2. The GDG also notes that age and presence of comorbidities of the patient may be a consideration in the decision of whether to conduct staging exams with imaging as this may change the choice of treatment.
3. Subgroups based on histological and marker results may impact the need to conduct staging examinations using imaging.

Adolopment

Sottogruppi basati sul tipo istologico e i risultati dei marcatori possono avere un impatto sul bisogno di effettuare esami di stadiazione con imaging

## Implementation considerations

Original

1. The GDG notes that a positive on imaging staging exams may be managed differently in different settings and in different body sites; if the presence of a distant metastasis on staging exams results in initiation of treatment, the impact of false positives may be greater.
2. The GDG considered the definition of 'clinical stage' as pre-pathological clinical stage, in accordance with the definition listed in the ECIBC glossary.
3. The GDG notes that there is still uncertainty with the evidence of detection rate using staging exams with imaging.
4. Consultation with colleagues during the interdisciplinary cancer treatment team meetings may be helpful in limiting the need for staging exams.
5. Education of healthcare providers to limit the use of staging exams using imaging for clinical stage IIa/IIb breast cancer.

Adolopment

Nessuna considerazione del panel

## Monitoring and evaluation

Original

1. The GDG suggests monitoring for compliance that routine staging exams using imaging are not conducted due to the undesirable effects, including increased false positives with small desirable effects.

Adolopment

Nessuna considerazione del panel

## Research priorities

Original

1. The GDG notes that no research evidence was identified on how people value the main outcomes. The GDG suggests additional research on how people value the main outcomes of staging exams for detection of metastases.
2. The GDG suggests further research on marker results and the implications for using staging exams using imaging.
3. Further research on the psychological effects and values and preferences for women related to the consequences of staging and non-staging approaches.

Adolopment

Nessuna considerazione del panel

## QUESITO 10

### Dovrebbe esami di stadiazione con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio II senza sintomi suggestivi di metastasi

POPULATION:	pazienti con cancro della mammella allo stadio II senza sintomi suggestivi di metastasi
INTERVENTION:	esami di stadiazione con 18F-FDG PET-CT
COMPARISON:	esami di stadiazione senza PET
MAIN OUTCOMES:	Detection rate; Falsi positivi;
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	<b>Conditional recommendation against the intervention</b> ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	---	---	--	---

## CONCLUSIONI

Original

## Recommendation

Per le pazienti con carcinoma mammario in stadio clinico IIa/IIb senza nessuna indicazione di metastasi, il panel suggerisce di non utilizzare la PET-CT per la stadiazione. (raccomandazione su condizione, certezza dell'evidenza molto bassa).

## Justification

The conditional recommendation for stage IIa, is a result of a balance that favours the comparison (no staging exams) with very low certainty of the evidence, so we are not very certain as to what the benefits are. In addition there are large costs, probably reduced equity and the intervention is probably not feasible. The GDG felt that very few situations would arise that would prompt conducting a PET-CT.

The conditional recommendation for stage IIb, is a result of a balance that does not favour PET-CT, with very low certainty of the evidence. In addition, the same as in stage IIa, there are large costs, probably reduced equity and the intervention is probably not feasible.

The concern about metastases that would not give symptoms in the life of a patient increases as breast cancer stages become lower.

Adolopment

## Recommendation

## Justification

## Subgroup considerations

Original

The GDG agreed that for stage IIb there are more scenarios (clinical presentations) that would lead the clinician/patient to opt for doing a PET-CT (tumour grade, age).

Adolopment

Nessuna considerazione del panel

## Implementation considerations

Original

None were considered by the GDG.

Adolopment

Nessuna considerazione del panel

## Monitoring and evaluation

Original

None were considered by the GDG.

Adolopment

Nessuna considerazione del panel

## Research priorities

Original

The GDG suggested the following:

- More knowledge on determining the probability of metastases that would not give symptoms in the life of a patient would improve describing the conditions for which PET-CT testing is indicated.
- Better characterisation of clinical tumour stages (stage IIa and stage IIb).

Adolopment

Nessuna considerazione del panel

## REFERENCES SUMMARY

### QUESITO 11

Dovrebbe esami convenzionali per la stadiazione vs nessun esame essere utilizzato per pazienti con cancro alla mammella al terzo stadio senza segni suggestivi per metastasi

<b>POPULATION:</b>	pazienti con cancro alla mammella al terzo stadio senza segni suggestivi per metastasi
<b>INTERVENTION:</b>	esami convenzionali per la stadiazione
<b>COMPARISON:</b>	nessun esame
<b>MAIN OUTCOMES:</b>	Detection rate: test combinati (prevalenza); Falsi positivi: test combinati; Detection rate: scintigrafia ossea; Falsi positivi: scintigrafia ossea; Detection rate: TC torace; Falsi positivi: TC torace; Detection rate: TC pelvi; Falsi positivi: TC pelvi; Detection rate: TC addome; Falsi positivi: TC addome; Detection rate: radiografia torace; Falsi positivi: radiografia torace; Detection rate: ecografia; Falsi positivi: ecografia
<b>SETTING:</b>	Italia
<b>PERSPECTIVE:</b>	Popolazione (Servizio Sanitario Nazionale)
<b>BACKGROUND:</b>	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
<b>CONFLICT OF INTEREST:</b>	<u>Gestione del conflitto di interesse (CoI)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## VALUTAZIONE

<b>Problem</b>		
Is the problem a priority?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The detection of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer and, in some cases, to start treatments that are specific for metastases</p> <p>Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, they are also associated with some disadvantages like limited specificity, leading to false positive with consequent psychological stress for the women, unnecessary ascertainment and, when ascertainment is not possible leading to wrong treatment planning; furthermore some imaging techniques have procedure related consequences, in particular radiation (depending on the used technique) and high costs.</p>	The GDG prioritised this question for the ECIBC.
	Adolopment	

<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

## Desirable Effects

How substantial are the desirable anticipated effects?

<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
----------------	--	----------------------------------

	Original	
--	----------	--

<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #0056b3; color: white;">Outcomes</th> <th style="background-color: #0056b3; color: white;">Impact</th> <th style="background-color: #0056b3; color: white;">N<sub>2</sub> of participants (studies)</th> <th style="background-color: #0056b3; color: white;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Detection rate: Combined tests (prevalence)</td> <td>Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510</td> <td>(5 RCTs)<sup>1,2,3,4,5</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,b,c,d</sup></td> </tr> <tr> <td>Detection rate: Bone Scan</td> <td>Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172</td> <td>(4 RCTs)<sup>2,3,6,7</sup></td> <td>⊕○○○ VERY LOW<sup>a,d,e,f</sup></td> </tr> <tr> <td>Detection rate: CT Chest</td> <td>Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417</td> <td>(1 RCT)<sup>8</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,e</sup></td> </tr> <tr> <td>Detection rate: CT pelvic - not reported</td> <td></td> <td>-</td> <td>-</td> </tr> <tr> <td>Detection rate: CT abdominal - not reported</td> <td></td> <td>-</td> <td>-<sup>a</sup></td> </tr> <tr> <td>Detection rate: XR Chest</td> <td>Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190</td> <td>(3 RCTs)<sup>2,3,9</sup></td> <td>⊕○○○ VERY LOW<sup>a,d,e,f</sup></td> </tr> <tr> <td>Detection rate: US</td> <td>Pooled detection rate: 57 per 1,000 examinations (95% CI: 12 - 157); n/N = 3/53</td> <td>(1 RCT)<sup>2</sup></td> <td>⊕⊕○○ LOW<sup>a,e,f</sup></td> </tr> </tbody> </table> <p style="margin-top: 10px;">1. Hulikal N, Gajjala SR, Kalawat TC, Kottu R, Amancharla Yadagiri L. Utility of [18F] Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT) in the Initial Staging and Response Assessment of Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy. Indian J Surg Oncol. ; 2015.</p>	Outcomes	Impact	N <sub>2</sub> of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>	Detection rate: Bone Scan	Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172	(4 RCTs) <sup>2,3,6,7</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>	Detection rate: CT Chest	Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417	(1 RCT) <sup>8</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>	Detection rate: CT pelvic - not reported		-	-	Detection rate: CT abdominal - not reported		-	- <sup>a</sup>	Detection rate: XR Chest	Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190	(3 RCTs) <sup>2,3,9</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>	Detection rate: US	Pooled detection rate: 57 per 1,000 examinations (95% CI: 12 - 157); n/N = 3/53	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,e,f</sup>	<p>In one study including 411 <b>clinical</b> stage II breast cancer patients (Bychkovsky 2016) evaluated by conventional imaging, the percentage of distant metastases did not differ by BC subtype: among ER/PR-positive and HER2-negative patients was 2.2% (95% CI, 0.5%–6.4%), for HER2+ patients was 1.9% (95% CI, 0%–9.9%), and in TNBC patients was 2.1% (95% CI, 0.1%–11.1%). Another study in 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (Groheux 2012), reported that the rates of distant metastases did not differ between TNBC (16%), HER2- positive (26%), and ER-positive (22%) breast cancers subtypes (p =0.42).</p> <p>The GDG agreed by consensus that the desirable effects were large.</p>
Outcomes	Impact	N <sub>2</sub> of participants (studies)	Certainty of the evidence (GRADE)																															
Detection rate: Combined tests (prevalence)	Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>																															
Detection rate: Bone Scan	Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172	(4 RCTs) <sup>2,3,6,7</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>																															
Detection rate: CT Chest	Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417	(1 RCT) <sup>8</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>																															
Detection rate: CT pelvic - not reported		-	-																															
Detection rate: CT abdominal - not reported		-	- <sup>a</sup>																															
Detection rate: XR Chest	Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190	(3 RCTs) <sup>2,3,9</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>																															
Detection rate: US	Pooled detection rate: 57 per 1,000 examinations (95% CI: 12 - 157); n/N = 3/53	(1 RCT) <sup>2</sup>	⊕⊕○○ LOW <sup>a,e,f</sup>																															



	<ol style="list-style-type: none"> <li>2. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andretta C, Di Terlizzi S, Piga A.. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications.. Ann Oncol. ; 2005.</li> <li>3. Dillman RO, Chico S.. Radiologic tests after a new diagnosis of breast cancer.. Eff Clin Pract.; 2000.</li> <li>4. Ravaioli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.</li> <li>5. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.</li> <li>6. Koizumi M, Yoshimoto M, Kasumi F, Ogata E.. What do breast cancer patients benefit from staging bone scintigraphy?. Jpn J Clin Oncol.; 2001.</li> <li>7. Lee JE, Park SS, Han W, Kim SW, Shin HJ, Choe KJ, Oh SK, Youn YK, Noh DY, Kim SW.. The clinical use of staging bone scan in patients with breast carcinoma: reevaluation by the 2003 American Joint Committee on Cancer staging system.. Cancer. ; 2005.</li> <li>8. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.</li> <li>9. Louie RJ, Tonneson JE, Gowarty M, Goodney PP, Barth RJ Jr, Rosenkranz KM.. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost?. Breast Cancer Res Treat.; 2015.</li> </ol> <ol style="list-style-type: none"> <li>a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.</li> <li>b. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimate the exams' performance. All studies reported to include follow-up of patients although with different time frame.</li> <li>c. Imaging for searching distant metastases is routine practice, therefore the risk of selected patient population undergoing staging is low also for retrospective studies.</li> <li>d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.</li> <li>e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance.</li> <li>f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.</li> </ol>	
--	---	--

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
False positive: Combined tests (prevalence)	Pooled false positive rate: 56 per 1,000 examinations (95%CI 33 - 84); n/N = 24/327	(2 RCTs) <sup>1,2</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>
False positive: Bone Scan - not reported		-	- <sup>a</sup>
False positive: CT Chest	False positive: 141 per 1,000 examinations (95%CI 109 - 179); n/N = 59/417	(1 RCT) <sup>3</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>
False positive: CT pelvic - not reported		-	-
False positive: CT abdominal - not reported		-	-
False positive: XR Chest	False positive: 60 per 1,000 examinations (95%CI 20 - 133); n/N = 5/84	(1 RCT) <sup>4</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>
False positive: US - not reported		-	-

1. Ravaioli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.
  2. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  3. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.
  4. Louie RJ, Tonneson JE, Gowarty M, Goodney PP, Barth RJ Jr, Rosenkranz KM.. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost?. Breast Cancer Res Treat.; 2015.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.
  - b. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - c. Imaging for searching distant metastases is routine practice, therefore the risk of selected patient population undergoing staging is low also for retrospective studies.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.

	<ul style="list-style-type: none"> <li>e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance.</li> <li>f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.</li> </ul>	
--	--	--

	Adolopment	
--	------------	--

<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>● Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

<b>Undesirable Effects</b> How substantial are the undesirable anticipated effects?		
--	--	--

<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
----------------	--	----------------------------------

	Original	
--	----------	--

<ul style="list-style-type: none"> <li>● Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<table border="1"> <thead> <tr> <th style="background-color: #2e75b6; color: white;">Outcomes</th> <th style="background-color: #d9d9d9;">Impact</th> <th style="background-color: #d9d9d9;">No of participants (studies)</th> <th style="background-color: #2e75b6; color: white;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Detection rate: Combined tests (prevalence)</td> <td>Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510</td> <td>(5 RCTs)<sup>1,2,3,4,5</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,b,c,d</sup></td> </tr> <tr> <td>Detection rate: Bone Scan</td> <td>Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172</td> <td>(4 RCTs)<sup>2,3,6,7</sup></td> <td>⊕○○○ VERY LOW<sup>a,d,e,f</sup></td> </tr> <tr> <td>Detection rate: CT Chest</td> <td>Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417</td> <td>(1 RCT)<sup>8</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,e</sup></td> </tr> <tr> <td>Detection rate: CT pelvic - not reported</td> <td></td> <td>-</td> <td>-</td> </tr> <tr> <td>Detection rate: CT abdominal - not reported</td> <td></td> <td>-</td> <td>-<sup>a</sup></td> </tr> <tr> <td>Detection rate: XR Chest</td> <td>Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190</td> <td>(3 RCTs)<sup>2,3,9</sup></td> <td>⊕○○○ VERY LOW<sup>a,d,e,f</sup></td> </tr> </tbody> </table>			Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>	Detection rate: Bone Scan	Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172	(4 RCTs) <sup>2,3,6,7</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>	Detection rate: CT Chest	Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417	(1 RCT) <sup>8</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>	Detection rate: CT pelvic - not reported		-	-	Detection rate: CT abdominal - not reported		-	- <sup>a</sup>	Detection rate: XR Chest	Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190	(3 RCTs) <sup>2,3,9</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>	<p>Sensitivity analysis without Puglisi (2005):          *Pooled false positive rate: 163.2 per 1000 examinations (95%CI 46.9 - 321.4); n/N = 46/309.</p> <p>The GDG agreed by consensus that the undesirable effects would be large.</p>	
	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)																													
	Detection rate: Combined tests (prevalence)	Pooled detection rate: 142 per 1,000 examinations (95%CI 113 - 175); n/N = 74/510	(5 RCTs) <sup>1,2,3,4,5</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>																													
	Detection rate: Bone Scan	Pooled detection rate: 103 per 1,000 examinations (95%CI: 53 - 167); n/N = 103/1,172	(4 RCTs) <sup>2,3,6,7</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>																													
	Detection rate: CT Chest	Pooled detection rate: 60 per 1,000 examinations (95%CI: 39 - 87); n/N = 25/417	(1 RCT) <sup>8</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>																													
	Detection rate: CT pelvic - not reported		-	-																													
	Detection rate: CT abdominal - not reported		-	- <sup>a</sup>																													
Detection rate: XR Chest	Pooled detection rate: 63 per 1,000 examinations (95% CI 16 - 131); n/N = 12/190	(3 RCTs) <sup>2,3,9</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>																														

Detection rate: US

Pooled detection rate: 57 per 1,000 examinations (95% CI: 12 - 157); n/N = 3/53

(1 RCT)<sup>2</sup>



1. Hulikal N, Gajjala SR, Kalawat TC, Kottu R, Amancharla Yadagiri L.. Utility of [18F] Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT) in the Initial Staging and Response Assessment of Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy.. Indian J Surg Oncol. ; 2015.
  2. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andretta C, Di Terlizzi S, Piga A.. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications.. Ann Oncol. ; 2005.
  3. Dillman RO, Chico S.. Radiologic tests after a new diagnosis of breast cancer.. Eff Clin Pract.; 2000.
  4. Ravaoli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.
  5. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  6. Koizumi M, Yoshimoto M, Kasumi F, Ogata E.. What do breast cancer patients benefit from staging bone scintigraphy?. Jpn J Clin Oncol.; 2001.
  7. Lee JE, Park SS, Han W, Kim SW, Shin HJ, Choe KJ, Oh SK, Youn YK, Noh DY, Kim SW.. The clinical use of staging bone scan in patients with breast carcinoma: reevaluation by the 2003 American Joint Committee on Cancer staging system.. Cancer. ; 2005.
  8. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.
  9. Louie RJ, Tonneson JE, Gowarty M, Goodney PP, Barth RJ Jr, Rosenkranz KM.. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost?. Breast Cancer Res Treat.; 2015.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.
  - b. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimate the exams' performance. All studies reported to include follow-up of patients although with different time frame.
  - c. Imaging for searching distant metastases is routine practice, therefore the risk of selected patient population undergoing staging is low also for retrospective studies.
  - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.
  - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance.

- f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive: Combined tests (prevalence)	Pooled false positive rate: 56 per 1,000 examinations (95%CI 33 - 84); n/N = 24/327	(2 RCTs) <sup>1,2</sup>	⊕⊕⊕○ MODERATE <sup>a,b,c,d</sup>
False positive: Bone Scan - not reported		-	- <sup>a</sup>
False positive: CT Chest	False positive: 141 per 1,000 examinations (95%CI 109 - 179); n/N = 59/417	(1 RCT) <sup>3</sup>	⊕⊕⊕○ MODERATE <sup>a,e</sup>
False positive: CT pelvic - not reported		-	-
False positive: CT abdominal - not reported		-	-
False positive: XR Chest	False positive: 60 per 1,000 examinations (95%CI 20 - 133); n/N = 5/84	(1 RCT) <sup>4</sup>	⊕○○○ VERY LOW <sup>a,d,e,f</sup>
False positive: US - not reported		-	-

1. Ravaoli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.
  2. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.
  3. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.
  4. Louie RJ, Tonneson JE, Gowarty M, Goodney PP, Barth RJ Jr, Rosenkranz KM.. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost?. Breast Cancer Res Treat.; 2015.
- a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.
- b. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.

	<ul style="list-style-type: none"> <li>c. Imaging for searching distant metastases is routine practice, therefore the risk of selected patient population undergoing staging is low also for retrospective studies.</li> <li>d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) which could or could not have symptoms suggestive of metastases.</li> <li>e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance.</li> <li>f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.</li> </ul>	
	Adolopment	
<ul style="list-style-type: none"> <li>● Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
<b>Certainty of evidence</b> What is the overall certainty of the evidence of effects?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		The GDG agreed by consensus that the certainty of the evidence of effects was moderate.
	Adolopment	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

Values		
Is there important uncertainty about or variability in how much people value the main outcomes?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>		<p>No systematic review for values and preferences regarding diagnostic exams was conducted.</p> <p>The GDG judged by consensus that there was possibly important uncertainty or variability.</p>
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
Balance of effects		
Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input type="radio"/> Probably favors the intervention</li> <li><input checked="" type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		<p>Voting was conducted because agreement was not reached consensus.</p> <p>*19 members voted in favour of 'favours the intervention'</p> <p>*2 members voted for 'probably favours the intervention', *2 members abstained and, *2 member was absent for the voting.</p>
	Adolopment	

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>● Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	<p>Il Panel ritiene che il vantaggio nel valore predittivo positivo sia prevalente rispetto all'importanza data al verificarsi di falsi positivi; pertanto, l'intervento risulterebbe più vantaggioso</p>
--	---	---

## Resources required

How large are the resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE															
	Original																
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>Direct evidence: Mean cost and utilization</b></p> <p>One Italian study (DePlacido 2017) determined the relative costs of staging and follow-up tests in a population of breast cancer patients in a Southern Italian region. The number and type of tests per patient were recorded 3 months before and 12 months after the date diagnosis of nonmetastatic breast cancer from 2001 to 2010.</p> <table border="1" data-bbox="551 847 1509 1238"> <thead> <tr> <th rowspan="2">Type of tests</th> <th colspan="3">Estimated annual variation (2001-2010)</th> </tr> <tr> <th>Mean cost<sup>1</sup> of imaging tests per patient (Euros)</th> <th>Imaging utilization, % (95% CI)</th> <th>Imaging-related costs, % (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Chest radiograph, abdominal ultrasound, bone scan, and mammograms</td> <td>Remain constant at 250 €</td> <td>Increase 0.1% (-0.1-0.3)</td> <td>Decrease 0.1% (-0.9 to 0.6)</td> </tr> <tr> <td>CT, PET, and MRI</td> <td>Increased from 350 € in 2001 to 800 € in 2010</td> <td>Increase 15.7% (14.2-17.2)</td> <td>Increase 19.4% (15.9-23.0)</td> </tr> </tbody> </table> <p><sup>1</sup>Prices were reported in 2011 Euros value.</p>	Type of tests	Estimated annual variation (2001-2010)			Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)	Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1-0.3)	Decrease 0.1% (-0.9 to 0.6)	CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2-17.2)	Increase 19.4% (15.9-23.0)	<p><b>Indirect evidence:</b> One study from Canada and two studies from the USA reported costs of imaging tests. The Canadian study reported that patients with stage II incurred higher imaging costs than those with stage I: CAD 535 per capita compared with CAD 204 per capita (2015 Canadian dollars) (Thavorn2016). The USA studies reported that the unitary cost per chest x-rays was USD 96.9, abdominal ultrasound USD 285, CT chest with contrast USD 239 to USD 510, CT abdominal-pelvis with contrast USD 305 to USD 696, body bone scan USD 658 to USD 853.8 (2013-2014 US dollars) (Louie2015, Pellet2016).</p> <p>The costs were lower than the cost for stage 2 staging exams using imaging.</p> <p>The GDG also notes that the number of patients presenting in this group (stage III) constitutes a smaller population.</p> <p>The GDG agreed by consensus that the resources required were moderate.</p>
Type of tests	Estimated annual variation (2001-2010)																
	Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)														
Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1-0.3)	Decrease 0.1% (-0.9 to 0.6)														
CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2-17.2)	Increase 19.4% (15.9-23.0)														



**Direct evidence: Unitary cost and cost of detecting metastatic disease**

One UK study (Barret 2009) estimated the health-care costs of detecting metastases by stage of disease and mode of imaging staging in a population of 3,398 newly diagnosed breast cancer patients during 1999 to 2007. The estimation was based on local costing taking into consideration staffing, consumable and hardware expenses. Calculations were carried out based on the observed true-positive rates and the added expense generated by false-positive imaging results.

Type of tests	Unitary cost <sup>1</sup> (British Pounds)	Cost <sup>1</sup> of detecting 1 patient with metastatic disease by breast cancer stage
		III
Chest radiograph	80 £	4,021 £
Ultrasound liver	176 £	
Bone scan	184 £	
CT (chest, abdomen, and pelvis)	271 £	2,405 £

<sup>1</sup>Value prices were not clearly reported (data was collected from 1999 to 2007).

Adolopment

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

Non sono state considerate evidenze di contesto per l'Italia

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Low certainty of the evidence due to indirectness, and imprecision. Costs reported in the studies may not be representative of other European settings since they were performed only in Campania, Italy or in the UK. For the UK study, in addition, value prices were not reported (data was collected from 1999 to 2007) and may not represent current costs. Also, there is imprecision in the results since the cost of each test was not reported.	The cost requirement evidence was based only on two studies with serious concerns regarding the indirectness and imprecision. The GDG judged that the certainty of evidence of required resources was low.
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input checked="" type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Basso livello delle evidenze anche a causa della variabilità dei protocolli applicati e applicabili sul territorio nazionale (che in alcuni casi potrebbero portare a costi maggiori)

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	No relevant economic evaluations were identified.	
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		<p>The GDG notes that due to a smaller population size there is a lower impact on equity.</p> <p>The GDG agreed by consensus that there would be probably no impact on health equity.</p>
	Adolopment	
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento è già raccomandato e offerto in Italia

## Acceptability

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The GDG agreed by consensus that it would probably be acceptable.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento è già proposto in Italia come prassi e accettato dalle donne

## Feasibility

Is the intervention feasible to implement?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The GDG agreed by consensus that it would probably be feasible.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento viene fornito di prassi in Italia

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLPMENT
PROBLEM	Yes	Yes
DESIRABLE EFFECTS	Large	Large
UNDESIRABLE EFFECTS	Large	Large
CERTAINTY OF EVIDENCE	Moderate	Moderate
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Favors the intervention	Favors the intervention
RESOURCES REQUIRED	Moderate costs	Moderate costs
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Low	Low
COST EFFECTIVENESS	No included studies	No included studies

<b>CRITERI</b>	<b>ORIGINAL</b>	<b>ADOLOPMENT</b>
<b>EQUITY</b>	Probably no impact	Probably no impact
<b>ACCEPTABILITY</b>	Probably yes	Probably yes
<b>FEASIBILITY</b>	Probably yes	Probably yes

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
---	--	---	--	---

## CONCLUSIONI

Original

### Recommendation

The ECIBC's Guidelines Development Group recommends using conventional staging exams with imaging in women with clinical stage III breast cancer (strong recommendation, moderate certainty of the evidence). (strong recommendation, moderate certainty of the evidence).

### Justification

#### Overall justification

Voting was conducted as agreement was not reached by consensus: 20 members (91%) for 'strong recommendation for the intervention', 2 members (9%) voted for 'conditional recommendation for the intervention'.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects were large with a pooled detection rate for combined tests of 142 per 1,000 examinations for women with stage III breast cancer.

##### *Undesirable Effects*

The GDG judged that the false positives contribute to large undesirable anticipated effects, however, notes that false positives are of lower concern for women with stage III breast cancer.

##### *Certainty of evidence*

The GDG judged that the certainty of the evidence of effects was moderate.

##### *Balance of effects*

The GDG judged that the balance of effects favours the intervention.

##### *Resources required*

The GDG judged that there would be moderate resources required for this intervention.

Adolopment

### Recommendation

Il panel raccomanda di utilizzare esami di stadiazione convenzionali nelle donne con cancro della mammella in stadio III (raccomandazione forte, moderata certezza delle evidenze)

### Justification

#### Overall justification

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable effects were large with a pooled detection rate for combined tests of 142 per 1,000 examinations for women with stage III breast cancer.

#### *Undesirable Effects*

The GDG judged that the false positives contribute to large undesirable anticipated effects, however, notes that false positives are of lower concern for women with stage III breast cancer.

#### *Certainty of evidence*

The GDG judged that the certainty of the evidence of effects was moderate.

#### *Balance of effects*

The GDG judged that the balance of effects favours the intervention.

#### *Resources required*

The GDG judged that there would be moderate resources required for this intervention.

## Subgroup considerations

Original

The GDG also notes that age and presence of comorbidities of the patient may be a consideration in the decision of whether to conduct staging exams with imaging as this may change the choice of treatment.

Adolopment

L'età e la presenza di comorbidità possono essere prese in considerazione nel decidere se effettuare esami di stadiazione con imaging in quanto possono modificare la scelta del trattamento

## Implementation considerations

Original

None considered.

1. The GDG considered the definition of stage groups according to the American Joint Commission on Cancer TNM Anatomic Stage Groups (8th ed.) listed in the ECIBC glossary.

Adolopment

Il panel suggerisce di utilizzare l'8th edizione del TNM per la stadiazione

## Monitoring and evaluation

Original

The GDG suggests monitoring that women with **clinical** stage III breast cancer receive staging exams using imaging.

Adolopment

Si suggerisce di monitorare che le donne con stadio clinico III ricevano esami di stadiazione con imaging

## Research priorities

Original

1. The GDG suggests research assessing the cause of false positive cases to minimize the number of false positives and the undue stress that this poses on patients with **clinical** stage III breast cancer.

2. The GDG suggests research on non-ionizing and low-radiation dose alternatives for staging exams using imaging.

1. Si raccomanda di effettuare ricerca sulle cause di falsi positivi per minimizzare il numero dei falsi positivi e lo stress correlato che subiscono le pazienti con stadio clinico III
2. Si raccomanda di effettuare ricerca su alternative senza uso di radiazioni ionizzanti o con radiazioni a bassa dose

## REFERENCES SUMMARY



## QUESITO 12

### Dovrebbe esami con 18F-FDG PET-CT vs esami di stadiazione senza PET essere utilizzato per pazienti con cancro della mammella allo stadio III senza sintomi suggestivi di metastasi

POPULATION:	pazienti con cancro della mammella allo stadio III senza sintomi suggestivi di metastasi
INTERVENTION:	esami con 18F-FDG PET-CT
COMPARISON:	esami di stadiazione senza PET
MAIN OUTCOMES:	Detection rate aggiuntiva (negativo vs. esami di stadiazione convenzionale); Detection rate; Falsi positivi
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
CONFLICT OF INTEREST:	Gestione del conflitto di interesse (CoI): Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## VALUTAZIONE

Problem		
Is the problem a priority?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>The main cause of death from breast cancer is distant metastases. The detection of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer. However, the risk for metastases is lower in early detected (clinical stage I and II) breast cancer than in later clinical stages (stage 3). Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, it is also associated with some disadvantages like limited specificity, leading to psychological stress of the women, radiation (depending on the used technique) and high costs.</p>	<p>The GDG prioritised this question for the ECIBC.</p>

	Adolpment													
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia													
<b>Desirable Effects</b> How substantial are the desirable anticipated effects?														
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>												
	Original													
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #4f81bd; color: white;">Outcomes</th> <th style="background-color: #d9d9d9;">Impact</th> <th style="background-color: #4f81bd; color: white;">№ of participants (studies)</th> <th style="background-color: #4f81bd; color: white;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Additional Detection rate (negative to conventional staging exams)</td> <td>Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382</td> <td>(7 RCTs)<sup>1,2,3,4,5,6,7</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,b</sup></td> </tr> <tr> <td>Detection rate</td> <td>*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.</td> <td>(8 RCTs)<sup>10,11,12,13,14,4,8,9,c</sup></td> <td>⊕○○○ VERY LOW<sup>a,b,d</sup></td> </tr> </tbody> </table> <ol style="list-style-type: none"> <li>Reddy Akepati NK, Abubakar ZA, Bikkina P. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018.</li> <li>Krammer J, Schnitzer A, Kaiser CG, Buesing KA, Sperk E, Brade J, Wasgindt S, Suetterlin M, Schoenberg SO, Sutton EJ, Wasser K.. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015.</li> <li>Ng SP, David S, Alamgeer M, Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015.</li> <li>Sen, F., Akpinar, A. T., Ogur, U., Duman, G., Tamgac, F., Alper, E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; Jun 2013.</li> <li>Manohar, K., Mittal, B. R., Bhoil, A., Bhattacharya, A., Singh, G.. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl Med Commun; Jun 2013.</li> </ol>	Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>	Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>	<p>Comparing the number of false positive indirectly (difference between false positives in 18FDG-PET/CT and conventional), from different studies, we considered that there would be around 61 fewer false positives cases per 1 000 women assessed with 18FDG-PET/CT. The subgroup analysis did not find differences in the rate of distant metastases (per 1000 examined patients) at clinical stage III, between women with triple negative breast cancer (TNBC) (DR: 255.9; 95% CI: 170.8 - 350.9) and the general breast cancer population (DR 338.3; 95% CI: 247.4 - 435.3) (Test heterogeneity: <i>p value</i> = 0.20).</p> <p>One study did not reveal significant differences in the rate of distant metastases at clinical stages I to III between breast cancer patients less than 40 years versus those ≥40 years (<i>p value</i>=1.0).</p> <p>Two studies reported false positives rates for patients in clinical stage II and III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1 000 examined women.</p> <p>One study in 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (Groheux 2012), reported that the rates of distant metastases did not differ between TNBC (16 %), HER2- positive (26 %), and ER- positive (22 %) breast cancers subtypes (<i>p</i> =0.42).</p>
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)											
Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>											
Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>											

	<ol style="list-style-type: none"> <li>6. Groheux, D., Moretti, J. L., Baillet, G., Espie, M., Giacchetti, S., Hindie, E., Hennequin, C., Vilcoq, J. R., Cuvier, C., Toubert, M. E., Filmont, J. E., Sarandi, F., Misset, J. L.. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. <i>Int J Radiat Oncol Biol Phys</i>; Jul 1 2008.</li> <li>7. Cochet, A., Dygai-Cochet, I., Riedinger, J. M., Humbert, O., Berriolo-Riedinger, A., Toubreau, M., Guiu, S., Coutant, C., Coudert, B., Fumoleau, P., Brunotte, F. (1)(8)F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. <i>Eur J Nucl Med Mol Imaging</i>; Mar 2014.</li> <li>8. Groheux, D., Hindie, E., Delord, M., Giacchetti, S., Hamy, A. S., de Bazelaire, C., de Roquancourt, A., Vercellino, L., Toubert, M. E., Merlet, P., Espie, M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. <i>J Natl Cancer Inst</i>; Dec 19 2012.</li> <li>9. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. <i>Eur J Nucl Med Mol Imaging</i>; Oct 2016.</li> <li>10. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. <i>J Nucl Med</i>; Oct 2014.</li> <li>11. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. <i>J Nucl Med</i>; Feb 2017.</li> <li>12. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. <i>J Nucl Med</i>; Nov 2015.</li> <li>13. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetskova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. <i>J Nucl Med</i>; 2009.</li> <li>14. Ulaner, G. A., Castillo, R., Goldman, D. A. 18F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. <i>Eur J Nucl Med Mol</i> ; 2017.</li> </ol> <ol style="list-style-type: none"> <li>a. Different reference standards were used across studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>b. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procedures and quality of data.</li> <li>c. Seven studies included in the pooled analysis for 18F-FDG PET/CT, and 5 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>d. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> </ol>	<p>The clinical impact of detecting distant metastasis (in practice moving the patient to Stage IV) can be considered on two domains:</p> <p><b>Survival</b> The 5-year relative survival rate for women with breast cancer by stage is approximately: -Stage III breast cancer is about 72% -Metastatic, or stage IV breast cancers survival rate of about 22%.</p> <p><b>Quality of life</b> This domain is influenced by the change of treatment plans in each clinical stage according to the presence of distant metastases: -Clinical stage III: potentially meaningful change depending on: 1) ER/PR positive/HER2 negative breast cancer: endocrine treatment only, no chemotherapy 2) HER positive: less intense chemotherapy regime; 3) triple negative: only mono-chemotherapy instead of poly-chemotherapy. Radiotherapy might or might not be indicated to primary lesion and in single cases of oligometastases. On those HER2+ possibly addition of Pertuzumab to the anti-HER2 therapy.</p> <p><b>PET/CT impact after Conventional Tests (Cochet 2013)</b></p> <p>The PET/CT results were believed to have high impact on 16 patients (11%). This group included four patients (3 %) for whom only palliative therapy was initially considered and then received curative treatment after PET/CT suggested absence of distant lesions</p> <p><b>Glycolytic activity with 18F-FDG PET/CT, tumour biology, and prognosis (Aroztegui 2017, Systematic Review)</b></p> <p><i>"Maximum standardised uptake value (SUVmax) increases with the biological aggressiveness of the tumours; high-grade, hormone receptor-negative, have higher SUVmax. However, a reproducible SUVmax cutoff that would predict tumour biology has yet to be established"</i></p>
--	--	---

*"The prognostic impact of the SUVmax of the primary tumour is controversial. Whereas some authors found no association between tumour 18F-FDG uptake and prognosis, others reported that patients with high tumour uptake had worse outcomes. Furthermore, a single and reproducible SUVmax has yet to be established"*

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328.    *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. <sup>a</sup>	(4 RCTs) <sup>1,2,3,4b</sup>	⊕○○○ VERY LOW <sup>c,d,e,f,g</sup>

The focus of the desirable effects for the GDG was on the additional 205 metastases detected per 1000 women using PET staging on those women negative to Conventional staging as well as the 61 fewer false positives with PET.

As there was disagreement among GDG members regarding whether the effects were large or moderate, voting took place among the GDG members without conflict of interest: 3 GDG members voted that the effects were "moderate"; 14 GDG members voted that the effects were "large".

1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.
  2. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.
  3. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.
  4. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009.
- a. Two studies reported false positives rates for patients in stage II/III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.
  - b. Four studies included in the pooled analysis for 18F-FDG PET/CT, and 4 studies for conventional tests (see ref in the technical report for conventional tests).
  - c. Different reference standards were used across studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.
  - d. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procediments and quality of data.
  - e. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.
  - f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision.
  - g. Overall studies included small sample sizes, therefore confidence interval are widen.

Adolopment

<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	
--	--	--

## Undesirable Effects


How substantial are the undesirable anticipated effects?

<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
----------------	--	----------------------------------

	Original	
--	----------	--

<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #0056b3; color: white;"> <th style="width: 25%;">Outcomes</th> <th style="width: 30%;">Impact</th> <th style="width: 15%;">No of participants (studies)</th> <th style="width: 30%;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Additional Detection rate (negative to conventional staging exams)</td> <td>Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382</td> <td>(7 RCTs)<sup>1,2,3,4,5,6,7</sup></td> <td>⊕⊕⊕○ MODERATE<sup>a,b</sup></td> </tr> <tr> <td>Detection rate</td> <td>*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.</td> <td>(8 RCTs)<sup>10,11,12,13,14,4,8,9,c</sup></td> <td>⊕○○○ VERY LOW<sup>a,b,d</sup></td> </tr> </tbody> </table> <ol style="list-style-type: none"> <li>1. Reddy Akepati NK, Abubakar ZA, Bikkina P. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018.</li> <li>2. Krammer J, Schnitzer A, Kaiser CG, Buesing KA, Sperk E, Brade J, Wasgindt S, Suetterlin M, Schoenberg SO, Sutton EJ, Wasser K.. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015.</li> <li>3. Ng SP, David S, Alamgeer M, Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015.</li> <li>4. Sen, F., Akpınar, A. T., Ogur, U., Duman, G., Tamgac, F., Alper, E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; Jun 2013.</li> <li>5. Manohar, K., Mittal, B. R., Bhoil, A., Bhattacharya, A., Singh, G.. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl Med Commun; Jun 2013.</li> <li>6. Groheux, D., Moretti, J. L., Baillet, G., Espie, M., Giacchetti, S., Hindie, E., Hennequin, C., Vilcoq, J. R., Cuvier, C., Toubert, M. E., Filmont, J. E., Sarandi, F., Misset, J.</li> </ol>	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>	Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>	<p>In Stage III, out of the 205 more detected, those overdiagnosed are going to be few. In Stage III, given the consistency with the survival data, the GDG was less concerned about overdiagnosis. That is, the proportion of metastases that would not give symptoms in the life of a patient will likely be very small, on the basis that we're already at Stage III breast cancer, although it cannot be estimated exactly; the GDG considered these less important given the limited impact on treatment and management decisions.</p> <p>Radiation is a possible adverse effect and radionuclide exposure.</p> <p>The GDG agreed by consensus that the undesirable effects would be trivial.</p>
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)											
Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>											
Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>											

	<p>L.. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. <i>Int J Radiat Oncol Biol Phys</i>; Jul 1 2008.</p> <ol style="list-style-type: none"> <li>7. Cochet, A., Dygai-Cochet, I., Riedinger, J. M., Humbert, O., Berriolo-Riedinger, A., Toubeau, M., Guiu, S., Coutant, C., Coudert, B., Fumoleau, P., Brunotte, F. (1)(8)F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. <i>Eur J Nucl Med Mol Imaging</i>; Mar 2014.</li> <li>8. Groheux, D., Hindie, E., Delord, M., Giacchetti, S., Hamy, A. S., de Bazelaire, C., de Roquancourt, A., Vercellino, L., Toubert, M. E., Merlet, P., Espie, M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. <i>J Natl Cancer Inst</i>; Dec 19 2012.</li> <li>9. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. <i>Eur J Nucl Med Mol Imaging</i>; Oct 2016.</li> <li>10. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. <i>J Nucl Med</i>; Oct 2014.</li> <li>11. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. <i>J Nucl Med</i>; Feb 2017.</li> <li>12. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. <i>J Nucl Med</i>; Nov 2015.</li> <li>13. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. <i>J Nucl Med</i>; 2009.</li> <li>14. Ulaner, G. A., Castillo, R., Goldman, D. A. 18F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. <i>Eur J Nucl Med Mol</i> ; 2017.</li> </ol> <ol style="list-style-type: none"> <li>a. Different reference standards were used across studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>b. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procedures and quality of data.</li> <li>c. Seven studies included in the pooled analysis for 18F-FDG PET/CT, and 5 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>d. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> </ol>	
--	--	--

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328.    *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. <sup>a</sup>	(4 RCTs) <sup>1,2,3,4b</sup>	 VERY LOW <sup>c,d,e,f,g</sup>
<ol style="list-style-type: none"> <li>1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</li> <li>2. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.</li> <li>3. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.</li> <li>4. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009.</li> </ol> <ol style="list-style-type: none"> <li>a. Two studies reported false positives rates for patients in stage II/III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.</li> <li>b. Four studies included in the pooled analysis for 18F-FDG PET/CT, and 4 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>c. Different reference standards were used accross studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>d. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procediments and quality of data.</li> <li>e. Event rates to assess 18F-FDG PET/CT and conventional tests were inderectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> <li>f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision.</li> <li>g. Overall studies included small sample sizes, therefore confidence interval are widen.</li> </ol>			
Adolpment			

<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>● Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
<b>Certainty of evidence</b>		
What is the overall certainty of the evidence of effects?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p>The evidence for correct diagnosis was considered moderate applying a testing framework.</p> <p>The GDG had moderate certainty that we are making the right diagnosis, but was not really certain about the downstream consequences. That is, whether these women classified as stage III, based on detection, are now receiving the appropriate treatment (ie. will they receive bisphosphonates if they have bone metastases).</p> <p>The GDG was uncertain about the effect this diagnostic test result has on treatment and the effect of this treatment (downstream consequences), so the overall certainty was judged as low.</p>
	Adolopment	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	L'incertezza sull'evidenza deriva dal grado di indirectness delle metriche usate rispetto all'outcome finale sul paziente.



## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>		The GDG agreed by consensus that there was possibly important uncertainty or variability.
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Important uncertainty or variability</li> <li><input checked="" type="radio"/> Possibly important uncertainty or variability</li> <li><input type="radio"/> Probably no important uncertainty or variability</li> <li><input type="radio"/> No important uncertainty or variability</li> <li><input type="radio"/> No known undesirable outcomes</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input checked="" type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>		The GDG agreed by consensus that the balance of effects probably favours the intervention.
	Adolopment	

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	
--	---	--

**Resources required**  
How large are the resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>PET/CT</b></p> <p>One study performed in the Netherlands (Koleva-Kolarova RG, 2015) reported the costs associated with implementing PET and PET/CT with FES or FDG as an upfront imaging test for diagnosing metastatic breast cancer in oestrogen receptor-positive women with symptoms. The reported unitary costs were:  CT: EUR 199  FES-PET: EUR 1 505  FDG-PET: EUR 1 505  The unit prices of the tests based on tariffs of The Dutch Healthcare Authority.</p> <p><b>Costs informed by the GDG</b></p>	<p>The cost per patient with stage III breast cancer receiving PET CT is about EUR 1 500 (only about 10% of all cancers are stage III, so only these will receive PET).</p> <p>The cost per patient with stage III breast cancer receiving conventional staging is about EUR 300 to 500.</p> <p>Therefore, the difference of receiving PET instead of conventional staging is EUR 1 000 to 1 200.</p> <p>As there was disagreement among GDG members regarding whether the effects were large or moderate, voting took place among the GDG members without conflict of interest: 14 GDG members voted that the costs were moderate; 3 GDG members voted that the costs were large.</p>

**Cost PET-CT**

Test	Country, year value	Setting	Cost
PET-CT staging*	Germany, 2017	Hospital	1987,76 Euro
PET alone	Germany, 2017	Hospital	1337,04 Euro
PET alone	Italy, 2012-2016	Hospital	1286,00 Euro

\* including all the cost for machine, radionuclide and the work of doctors and technicians

**Resources required PET-CT**

Resources	Cost
PET-CT machine	2.5 million Euro
Reactor to make the radionuclide	NA
Nuclear medicine doctor	NA
Radiologist	NA
Nurse/technician running the machine	NA
Medical physicist	NA

Conventional tests

**Direct evidence: Mean cost and utilization**

One Italian study (DePlacido 2017) determined the relative costs of staging and follow-up tests in a population of breast cancer patients in a Southern Italian region. The number and type of tests per patient were recorded 3 months before and 12 months after the date diagnosis of nonmetastatic breast cancer from 2001 to 2010.

Type of tests	Estimated annual variation (2001-2010)		
	Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)
Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1-0.3)	Decrease 0.1% (-0.9 to 0.6)
CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2-17.2)	Increase 19.4% (15.9-23.0)

<sup>1</sup>Prices were reported in 2011 Euros value.

**Direct evidence: Unitary cost and cost of detecting metastatic disease**

One UK study (Barret 2009) estimated the health-care costs of detecting metastases by stage of disease and mode of imaging staging in a population of 3,398 newly diagnosed breast cancer patients during 1999 to 2007. The estimation was based on local costing taking into consideration staffing, consumable and hardware expenses. Calculations were carried out based on the observed true-positive rates and the added expense generated by false-positive imaging results.

Type of tests	Unitary cost <sup>1</sup> (British Pounds)	Cost <sup>1</sup> of detecting 1 patient with metastatic disease by breast cancer stage
		III
Chest radiograph	80 £	4,021 £
Ultrasound liver	176 £	
Bone scan	184 £	
CT (chest, abdomen, and pelvis)	271 £	2,405 £

<sup>1</sup>Value prices were not clearly reported (data was collected from 1999 to 2007).

Adolopment

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

Il tariffario italiano riporta 1280 EUR per esame PET

## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Have direct information from hospitals in Europe.	The GDG agreed the certainty of the resources evidence was moderate.
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	No economic evaluations were identified	No studies were included .
	Adolopment	
<ul style="list-style-type: none"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed that equity would probably be reduced. In many countries there may be problems providing PET to these patients.
	Adolopment	
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	Diverse modalità organizzative permettono di offrire la prestazione su tutto il territorio italiano anche se in modo non omogeneo

## Acceptability

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed it was probably acceptable. The main concern for acceptability would be payers.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento è accettabile da parte delle donne

## Feasibility

Is the intervention feasible to implement?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed the feasibility would vary.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento può richiedere diversi assetti di organizzazione dell'offerta per essere garantito nei diversi territori

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	IMPORTANCE FOR DECISION	ADOLOPMENT	IMPORTANCE FOR DECISION
PROBLEM	Yes		Yes	
DESIRABLE EFFECTS	Large		Large	
UNDESIRABLE EFFECTS	Trivial		Trivial	
CERTAINTY OF EVIDENCE	Low		Low	
VALUES	Possibly important uncertainty or variability		Possibly important uncertainty or variability	
BALANCE OF EFFECTS	Probably favors the intervention		Probably favors the intervention	
RESOURCES REQUIRED	Moderate costs		Moderate costs	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Moderate		Moderate	
COST EFFECTIVENESS	No included studies		No included studies	



<b>CRITERI</b>	<b>ORIGINAL</b>	<b>IMPORTANCE FOR DECISION</b>	<b>ADOLOPMENT</b>	<b>IMPORTANCE FOR DECISION</b>
<b>EQUITY</b>	Probably reduced		Probably reduced	
<b>ACCEPTABILITY</b>	Probably yes		Probably yes	
<b>FEASIBILITY</b>	Varies		Varies	

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
---	--	---	---	---

## CONCLUSIONI

### Recommendation

For patients with clinical stage III breast cancer without symptoms suggestive of metastases, the ECIBC's Guidelines Development Group (GDG) suggests using positron emission tomography-computed tomography (PET-CT) over conventional staging exams (conditional recommendation, low certainty of the evidence).

**Per pazienti con cancro della mammella in stadio III senza sintomi suggestivi di metastasi, il panel suggerisce l'utilizzo della PET-CT rispetto allo staging convenzionale (raccomandazione su condizione, bassa certezza nelle evidenze)**

### Justification

The conditional recommendation is a result of a balance of effects that probably favours the intervention (PET-CT) but has moderate costs and probably reduces equity.

### Subgroup considerations

None were considered by the GDG .

Nessuna considerata dal panel

Original

Adolopment

### Implementation considerations

Need to take into account the resource capacity (including human resources and financial resources and equipment) across Europe.

È necessario tenere in conto le risorse (umane, finanziarie e tecnologiche) nelle diverse aree del paese. È importante che nei territori in cui l'intervento è disponibile sia offerto tempestivamente e in tutti i casi in cui è richiesto visto l'ampio beneficio atteso rispetto ai limiti

Original

Adolopment

### Monitoring and evaluation

None were considered by the GDG

Nessuna considerata dal panel

Original

Adolopment

## Research priorities

Original

- Need for cost-effectiveness data
- Need for studies evaluating follow-up of patients that would address patient important outcomes as the only data evaluated is on accuracy outcomes.

Adolopment

Sono necessari dati sulla costo-efficacia  
Sono necessari studi sui patient-reported outcomes poichè i soli dati valutati sono sull'accuratezza

## REFERENCES SUMMARY

## QUESITO 13

### Dovrebbe esami di stadiazione convenzionali seguiti da 18F-FDG PET-CT vs esami di stadiazione convenzionali essere utilizzato per pazienti con cancro della mammella clinicamente allo stadio III senza segni suggestivi di metastasi


POPULATION:	pazienti con cancro della mammella clinicamente allo stadio III senza segni suggestivi di metastasi
INTERVENTION:	esami di stadiazione convenzionali seguiti da 18F-FDG PET-CT
COMPARISON:	esami di stadiazione convenzionali
MAIN OUTCOMES:	Detection rate aggiuntiva (negativo vs. esami di stadiazione convenzionale); Detection rate; Falsi positivi
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	La principale causa di morte per cancro alla mammella è dovuta a metastasi a distanza. Il rilevamento di metastasi a distanza in pazienti con carcinoma mammario di nuova diagnosi modifica il trattamento e la prognosi. Se sono presenti metastasi, la prognosi peggiora significativamente e il trattamento deve trovare un equilibrio tra prolungamento della sopravvivenza e qualità della vita poiché la malattia non è più curabile. Pertanto, la stadiazione mira ad evitare il sovratrattamento nei pazienti con carcinoma mammario con metastasi primarie e, in alcuni casi, ad avviare trattamenti specifici per le metastasi. Tuttavia, il rischio di metastasi è inferiore nel carcinoma mammario rilevato precocemente (stadio clinico I e II) rispetto agli stadi successivi (stadio clinico III). Sebbene gli interventi di stadiazione abbiano il vantaggio di garantire un trattamento adeguato allo stadio del tumore, sono anche associati ad alcuni svantaggi come: specificità limitata, che porta a falsi positivi con conseguente stress psicologico per le donne, accertamenti non necessari e, quando l'accertamento non è possibile, portando a una pianificazione errata del trattamento; inoltre alcune tecniche di imaging hanno conseguenze legate alla procedura stessa, in particolare le radiazioni (a seconda della tecnica utilizzata) e costi elevati.
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## VALUTAZIONE

Problem		
Is the problem a priority?		
GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>The main cause of death from breast cancer is due to distant metastases. The detection of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly, and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer. However, the risk for metastases is lower in early detected (clinical stage I and II) breast cancer than in later clinical stages (stage 3). Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, it is also associated with some disadvantages like limited specificity, leading to psychological stress of the women, radiation (depending on the used technique) and high costs.</p>	The GDG prioritised this question for the ECIBC.

	Adolpment													
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia													
<b>Desirable Effects</b> How substantial are the desirable anticipated effects?														
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>												
	Original													
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #4f81bd; color: white;">Outcomes</th> <th style="background-color: #d9d9d9;">Impact</th> <th style="background-color: #4f81bd; color: white;">№ of participants (studies)</th> <th style="background-color: #4f81bd; color: white;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td style="background-color: #d9d9d9;">Additional Detection rate (negative to conventional staging exams)</td> <td style="background-color: #d9d9d9;">Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382</td> <td style="background-color: #d9d9d9;">(7 RCTs)<sup>1,2,3,4,5,6,7</sup></td> <td style="background-color: #d9d9d9;">⊕⊕⊕○ MODERATE<sup>a,b</sup></td> </tr> <tr> <td style="background-color: #d9d9d9;">Detection rate</td> <td style="background-color: #d9d9d9;">*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.</td> <td style="background-color: #d9d9d9;">(8 RCTs)<sup>10,11,12,13,14,4,8,9,c</sup></td> <td style="background-color: #d9d9d9;">⊕○○○ VERY LOW<sup>a,b,d</sup></td> </tr> </tbody> </table> <ol style="list-style-type: none"> <li>1. Reddy Akepati NK, Abubakar ZA, Bikkina P. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018.</li> <li>2. Krammer J, Schnitzer A, Kaiser CG, Buesing KA, Sperk E, Brade J, Wasgindt S, Suetterlin M, Schoenberg SO, Sutton EJ, Wasser K.. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015.</li> <li>3. Ng SP, David S, Alamgeer M, Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015.</li> <li>4. Sen, F., Akpinar, A. T., Ogur, U., Duman, G., Tamgac, F., Alper, E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; Jun 2013.</li> <li>5. Manohar, K., Mittal, B. R., Bhoil, A., Bhattacharya, A., Singh, G.. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl Med Commun; Jun 2013.</li> </ol>	Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>	Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>	<p>61 fewer false positives (difference between false positives in PET and conventional) if all women will undergo PET-CT.</p> <p>The subgroup analysis did not find difference in the rate of distant metastases (per 1000 examined patients) at clinical stage III, between women with triple negative breast cancer (TNBC) (DR: 255.9; 95% CI: 170.8 - 350.9) to general breast cancer population (DR 338.3; 95% CI: 247.4 - 435.3) (Test heterogeneity: <i>p value</i> = 0.20)</p> <p>One study did not reveal significant difference in the rate of distant metastases at clinical stages I to III between breast cancer patients less than 40 years versus those ≥40 years (<i>p value</i>=1.0).</p> <p>Two studies reported false positives rates for patients in clinical stage II and III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women. One study in 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (Groheux 2012), reported that the rates of distant metastases did not differ between TNBC (16 %), HER2- positive (26 %), and ER-positive (22 %) breast cancers subtypes (<i>p</i> =0.42).</p> <p>The clinical impact of detecting distant metastasis (in practice moving the patient to Stage IV) can be considered on two domains:</p> <p><u>Survival</u></p>
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)											
Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>											
Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>											

	<ol style="list-style-type: none"> <li>6. Groheux, D., Moretti, J. L., Baillet, G., Espie, M., Giacchetti, S., Hindie, E., Hennequin, C., Vilcoq, J. R., Cuvier, C., Toubert, M. E., Filmont, J. E., Sarandi, F., Misset, J. L.. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. <i>Int J Radiat Oncol Biol Phys</i>; Jul 1 2008.</li> <li>7. Cochet, A., Dygai-Cochet, I., Riedinger, J. M., Humbert, O., Berriolo-Riedinger, A., Toubeau, M., Guiu, S., Coutant, C., Coudert, B., Fumoleau, P., Brunotte, F. (1)(8)F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. <i>Eur J Nucl Med Mol Imaging</i>; Mar 2014.</li> <li>8. Groheux, D., Hindie, E., Delord, M., Giacchetti, S., Hamy, A. S., de Bazelaire, C., de Roquancourt, A., Vercellino, L., Toubert, M. E., Merlet, P., Espie, M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. <i>J Natl Cancer Inst</i>; Dec 19 2012.</li> <li>9. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. <i>Eur J Nucl Med Mol Imaging</i>; Oct 2016.</li> <li>10. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. <i>J Nucl Med</i>; Oct 2014.</li> <li>11. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. <i>J Nucl Med</i>; Feb 2017.</li> <li>12. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. <i>J Nucl Med</i>; Nov 2015.</li> <li>13. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetskova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. <i>J Nucl Med</i>; 2009.</li> <li>14. Ulaner, G. A., Castillo, R., Goldman, D. A. 18F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. <i>Eur J Nucl Med Mol</i> ; 2017. <ol style="list-style-type: none"> <li>a. Different reference standards were used across studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>b. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procedures and quality of data.</li> <li>c. Seven studies included in the pooled analysis for 18F-FDG PET/CT, and 5 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>d. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> </ol> </li> </ol>	<p>The 5-year relative survival rate for women with breast cancer by stage is approximately:  -Stage III breast cancer is about 72%  -Metastatic, or stage IV breast cancers survival rate of about 22%.</p> <p><u>Quality of life</u> This domain is influenced by the change of treatment plans in each clinical stage according to the presence of distant metastases:  -Clinical stage III: potentially meaningful change depending on: 1) ER/PR positive/HER2 negative breast cancer: endocrine treatment only, no chemotherapy 2) HER positive: less intense chemotherapy regime; 3) triple negative: only mono-chemotherapy instead of poly-chemotherapy. Radiotherapy might or might not be indicated to primary lesion and in single cases of oligometastases. On those HER2+ possibly addition of Pertuzumab to the anti-HER2 therapy.</p> <p><b>PET/CT impact after Conventional Tests (Cochet 2013)</b>  The PET/CT results were believed to have high impact on 16 patients (11%). This group included four patients (3 %) for whom only palliative therapy was initially considered and then received curative treatment after PET/CT suggested absence of distant lesions</p> <p><b>Glycolytic activity with 18F-FDG PET/CT, tumor biology, and prognosis (Aroztegui 2017, Systematic Review)</b>  <i>"Maximum standardized uptake value (SUVmax) increases with the biological aggressiveness of the tumors; high-grade, hormone receptor-negative, have higher SUVmax. However, a reproducible SUVmax cutoff that would predict tumor biology has yet to be established"</i>  <i>"The prognostic impact of the SUVmax of the primary tumor is controversial. Whereas some authors found no association between tumor 18F-FDG uptake and prognosis, others reported that patients with high tumor uptake had worse outcomes. Furthermore, a single and reproducible SUVmax has yet to be established"</i></p>
--	--	---

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328.    *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. <sup>a</sup>	(4 RCTs) <sup>1,2,3,4b</sup>	 VERY LOW <sup>c,d,e,f,g</sup>
<ol style="list-style-type: none"> <li>1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</li> <li>2. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.</li> <li>3. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.</li> <li>4. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009.</li> </ol> <ol style="list-style-type: none"> <li>a. Two studies reported false positives rates for patients in stage II/III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.</li> <li>b. Four studies included in the pooled analysis for 18F-FDG PET/CT, and 4 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>c. Different reference standards were used accross studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>d. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procediments and quality of data.</li> <li>e. Event rates to assess 18F-FDG PET/CT and conventional tests were inderectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> <li>f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision.</li> <li>g. Overall studies included small sample sizes, therefore confidence interval are widen.</li> </ol>			
Adolopment			
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large	Non sono state considerate evidenze di contesto per l'Italia		

<ul style="list-style-type: none"> <li>○ Varies</li> <li>○ Don't know</li> </ul>		
--	--	--

## Undesirable Effects

How substantial are the undesirable anticipated effects?


GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
---------	---------------------------------	---------------------------

	Original	
--	----------	--

<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>● Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #0056b3; color: white;">Outcomes</th> <th style="background-color: #d3d3d3;">Impact</th> <th style="background-color: #0056b3; color: white;">No of participants (studies)</th> <th style="background-color: #0056b3; color: white;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td style="background-color: #d3d3d3;">Additional Detection rate (negative to conventional staging exams)</td> <td style="background-color: #d3d3d3;">Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382</td> <td style="background-color: #d3d3d3;">(7 RCTs)<sup>1,2,3,4,5,6,7</sup></td> <td style="background-color: #d3d3d3;">⊕⊕⊕○ MODERATE<sup>a,b</sup></td> </tr> <tr> <td style="background-color: #d3d3d3;">Detection rate</td> <td style="background-color: #d3d3d3;">*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.</td> <td style="background-color: #d3d3d3;">(8 RCTs)<sup>10,11,12,13,14,4,8,9,c</sup></td> <td style="background-color: #d3d3d3;">⊕○○○ VERY LOW<sup>a,b,d</sup></td> </tr> </tbody> </table> <p style="margin-top: 10px;">1. Reddy Akepati NK, Abubakar ZA, Bikkina P. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018.</p> <p>2. Krammer J, Schnitzer A, Kaiser CG, Buesing KA, Sperk E, Brade J, Wasgindt S, Suetterlin M, Schoenberg SO, Sutton EJ, Wasser K.. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015.</p> <p>3. Ng SP, David S, Alamgeer M, Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015.</p> <p>4. Sen, F., Akpınar, A. T., Ogur, U., Duman, G., Tamgac, F., Alper, E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; Jun 2013.</p> <p>5. Manohar, K., Mittal, B. R., Bhoil, A., Bhattacharya, A., Singh, G.. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl Med Commun; Jun 2013.</p> <p>6. Groheux, D., Moretti, J. L., Baillet, G., Espie, M., Giacchetti, S., Hindie, E., Hennequin, C., Vilcoq, J. R., Cuvier, C., Toubert, M. E., Filmont, J. E., Sarandi, F., Misset, J. L.. Effect of (18)F-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. Int J Radiat Oncol Biol Phys; Jul 1 2008.</p> <p>7. Cochet, A., Dygai-Cochet, I., Riedinger, J. M., Humbert, O., Berriolo-Riedinger, A., Toubreau, M., Guiu, S., Coutant, C., Coudert, B., Fumoleau, P., Brunotte, F. (1)(8)F-</p>	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>	Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>	<p>The proportion of metastases that would not give symptoms in the life of a patient will likely be very small although it cannot be estimated exactly considered less important given the limited impact on treatment &amp; management decisions.</p> <p>Radiation is a possible adverse effect and radionuclide exposure.</p> <p>Carrying two tests (conventional staging and PET) compared to one (only conventional staging) can be considered an undesirable effect (extra examinations and additional radiation).</p>
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)											
Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) <sup>1,2,3,4,5,6,7</sup>	⊕⊕⊕○ MODERATE <sup>a,b</sup>											
Detection rate	*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627.    *Combined conventional test: 157 per 1,000 examinations (95% CI 125 -192); n/N = 74/465.	(8 RCTs) <sup>10,11,12,13,14,4,8,9,c</sup>	⊕○○○ VERY LOW <sup>a,b,d</sup>											



	<p>FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. Eur J Nucl Med Mol Imaging; Mar 2014.</p> <ol style="list-style-type: none"> <li>8. Groheux, D., Hindie, E., Delord, M., Giacchetti, S., Hamy, A. S., de Bazelaire, C., de Roquancourt, A., Vercellino, L., Toubert, M. E., Merlet, P., Espie, M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst; Dec 19 2012.</li> <li>9. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</li> <li>10. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.</li> <li>11. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. J Nucl Med; Feb 2017.</li> <li>12. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.</li> <li>13. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009.</li> <li>14. Ulaner, G. A., Castillo, R., Goldman, D. A. 18F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. Eur J Nucl Med Mol ; 2017.</li> </ol> <ol style="list-style-type: none"> <li>a. Different reference standards were used across studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>b. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procedures and quality of data.</li> <li>c. Seven studies included in the pooled analysis for 18F-FDG PET/CT, and 5 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>d. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> </ol>	
--	---	--

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328.    *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. <sup>a</sup>	(4 RCTs) <sup>1,2,3,4b</sup>	 VERY LOW <sup>c,d,e,f,g</sup>
<ol style="list-style-type: none"> <li>1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</li> <li>2. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.</li> <li>3. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.</li> <li>4. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetkova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009.</li> </ol> <ol style="list-style-type: none"> <li>a. Two studies reported false positives rates for patients in stage II/III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.</li> <li>b. Four studies included in the pooled analysis for 18F-FDG PET/CT, and 4 studies for conventional tests (see ref in the technical report for conventional tests).</li> <li>c. Different reference standards were used accross studies, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.</li> <li>d. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procediments and quality of data.</li> <li>e. Event rates to assess 18F-FDG PET/CT and conventional tests were inderectly compared. Studies differ in the number of patients, level of health care and time of follow-up.</li> <li>f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision.</li> <li>g. Overall studies included small sample sizes, therefore confidence interval are widen.</li> </ol>			
Adolopment			

<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>● Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	
<p><b>Certainty of evidence</b>          What is the overall certainty of the evidence of effects?</p>		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>		<p>The evidence for correct diagnosis was considered moderate applying a testing framework.</p> <p>The GDG had moderate certainty that we are making the right diagnosis, but was not really certain about the downstream consequences. That is, whether these women classified as stage III, based on detection, are now receiving the appropriate treatment (ie. will they receive bisphosphonates if they have bone metastases).</p> <p>The GDG was uncertain about the effect this diagnostic test result has on treatment and the effect of this treatment (downstream consequences), so the overall certainty was judged as low.</p>
	Adolopment	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability <input type="radio"/> No known undesirable outcomes		
	Adolopment	
<input type="radio"/> Important uncertainty or variability <input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability <input type="radio"/> No known undesirable outcomes	Non sono state considerate evidenze di contesto per l'Italia	

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know		
	Adolopment	

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Non sono state considerate evidenze di contesto per l'Italia</p>	
--	---	--

## Resources required

How large are the resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>● Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p><b>PET/CT</b></p> <p>One study performed in the Netherlands ((Koleva-Kolarova RG, 2015)) reported the costs associated with implementing PET and PET/CT with FES or FDG as an upfront imaging test for diagnosing metastatic breast cancer in oestrogen receptor-positive women with symptoms. The reported unitary costs were:</p> <p>CT: 199 €  FES-PET: 1.505 €  FDG-PET: 1.505 €</p> <p>The unit prices of the tests based on tariffs of The Dutch Healthcare Authority.</p> <p><b>Costs informed by the GDG</b></p>	<p>The cost per patient with Stage II breast cancer receiving PET- CT is about EUR 1500.</p> <p>The cost per patient receiving conventional testing is about EUR 300 to 500, but women in both intervention and comparison arm receive conventional testing.</p> <p>Total cost difference is the additional PET in the intervention arm which is EUR 1500.  Savings might result from more appropriate treatment.</p> <p>As there was disagreement among GDG members regarding whether the costs were large or moderate, voting took place among GDG members without conflict of interest:  11 members voted for "moderate costs" and six members voted for "large costs".</p>

**Cost PET-CT**

Test	Country, year value	Setting	Cost
PET-CT staging*	Germany, 2017	Hospital	1987,76 Euro
PET alone	Germany, 2017	Hospital	1337,04 Euro
PET alone	Italy, 2012-2016	Hospital	1286,00 Euro

\* including all the cost for machine, radionuclide and the work of doctors and technicians

**Resources required PET-CT**

Resources	Cost
PET-CT machine	2.5 million Euro
Reactor to make the radionuclide	NA
Nuclear medicine doctor	NA
Radiologist	NA
Nurse/technician running the machine	NA
Medical physicist	NA

Conventional tests

**Direct evidence: Mean cost and utilization**

One Italian study (DePlacido 2017) determined the relative costs of staging and follow-up tests in a population of breast cancer patients in a Southern Italian region. The number and type of tests per patient were recorded 3 months before and 12 months after the date diagnosis of nonmetastatic breast cancer from 2001 to 2010.

Type of tests	Estimated annual variation (2001-2010)		
	Mean cost <sup>1</sup> of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)
Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1-0.3)	Decrease 0.1% (-0.9 to 0.6)
CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2-17.2)	Increase 19.4% (15.9-23.0)

<sup>1</sup>Prices were reported in 2011 Euros value.

**Direct evidence: Unitary cost and cost of detecting metastatic disease**

One UK study (Barret 2009) estimated the health-care costs of detecting metastases by stage of disease and mode of imaging staging in a population of 3,398 newly diagnosed breast cancer patients during 1999 to 2007. The estimation was based on local costing taking into consideration staffing, consumable and hardware expenses. Calculations were carried out based on the observed true-positive rates and the added expense generated by false-positive imaging results.

Type of tests	Unitary cost <sup>1</sup> (British Pounds)	Cost <sup>1</sup> of detecting 1 patient with metastatic disease by breast cancer stage
		III
Chest radiograph	80 £	4,021 £
Ultrasound liver	176 £	
Bone scan	184 £	
CT (chest, abdomen, and pelvis)	271 £	2,405 £

<sup>1</sup>Value prices were not clearly reported (data was collected from 1999 to 2007).



Adolopment

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- Varies
- Don't know

Secondo il tariffario regionale, il rimborso per la PET total body in Emilia-Romagna corrisponde a 1286 euro a cui si aggiungono i costi degli esami individuali di stadiazione convenzionale



## Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Have direct information from hospitals in Europe.	The GDG agreed the certainty of the resources evidence was moderate.
	Adolopment	
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>● Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	No economic evaluations were identified	No studies were included.
	Adolopment	

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	
---	--	--

## Equity

What would be the impact on health equity?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No systematic review was carried out.	The GDG agreed that equity would probably be reduced. In many countries there may be problems providing PET to these patients.
	Adolopment	
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>● Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	Non sono state considerate evidenze di contesto per l'Italia	Diverse modalità organizzative permettono di offrire la prestazione su tutto il territorio italiano anche se in modo non omogeneo

## Acceptability

Is the intervention acceptable to key stakeholders?

GIUDIZI	RICERCA DELLE PROVE DI EVIDENZA	CONSIDERAZIONI AGGIUNTIVE
	Original	
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>● Probably yes</li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	No systematic review was carried out.	The GDG agreed it was probably acceptable. The main concern for acceptability would be payers.
	Adolopment	

<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento è accettabile da parte delle donne.
<b>Feasibility</b> Is the intervention feasible to implement?		
<b>GIUDIZI</b>	<b>RICERCA DELLE PROVE DI EVIDENZA</b>	<b>CONSIDERAZIONI AGGIUNTIVE</b>
	Original	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed the feasibility would vary.
	Adolopment	
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	Non sono state considerate evidenze di contesto per l'Italia	L'intervento può richiedere diversi assetti di organizzazione dell'offerta per essere garantito nei diversi territori. La valutazione di fattibilità è legata anche all'aggiunta degli altri esami di stadiazione.

## SUMMARY OF JUDGEMENTS

CRITERI	ORIGINAL	ADOLOPMENT
PROBLEM	Yes	Yes
DESIRABLE EFFECTS	Large	Large
UNDESIRABLE EFFECTS	Trivial	Trivial
CERTAINTY OF EVIDENCE	Low	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the intervention	Probably favors the intervention
RESOURCES REQUIRED	Moderate costs	Moderate costs

CRITERI	ORIGINAL	ADOLOPMENT
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Moderate	Moderate
COST EFFECTIVENESS	No included studies	No included studies
EQUITY	Probably reduced	Probably reduced
ACCEPTABILITY	Probably yes	Probably yes
FEASIBILITY	Varies	Varies

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	<b>Conditional recommendation for the intervention</b> ●	Strong recommendation for the intervention ○
---	--	---	---	---

## CONCLUSIONI

Original

### Recommendation

For patients with clinical stage III breast cancer without symptoms suggestive of metastases, the ECIBC's Guidelines Development Group (GDG) suggests using conventional staging followed by positron emission tomography-computed tomography (PET-CT) over conventional staging alone (conditional recommendation, low certainty of the evidence).

### Justification

The conditional recommendation is a result of a balance of effects that probably favours the intervention (conventional staging followed by PET-CT) but has moderate costs and probably reduces equity.

Adolopment

### Recommendation

**Per pazienti con cancro della mammella in stadio III senza sintomi suggestivi di metastasi, il panel suggerisce l'utilizzo di esami convenzionali di staging seguiti da PET-CT rispetto allo staging convenzionale da solo (raccomandazione su condizione, bassa certezza nelle evidenze)**

### Justification

Aggiungere il conventional staging alla PET CT non dà benefici e anzi aumenta i costi e i rischi dovuti ai test aggiuntivi fatti

### Subgroup considerations

Original

None were considered by the GDG.

Adolopment

Nessuna considerata dal panel

### Implementation considerations

Original

None were considered by the GDG.

 Adolopment

Un approccio direttamente con PET favorirebbe l'implementazione rispetto all'intervento con esami convenzionali + PET

## Monitoring and evaluation

 Original

None were considered by the GDG.

 Adolopment

Nessuna considerata dal panel

## Research priorities

 Original

None were considered by the GDG.

 Adolopment

Nessuna considerata dal panel

## REFERENCES SUMMARY

## QUESITO 14

### Dovrebbe una soglia del 10% o più vs 1% o più cellule positive per il recettore degli estrogeni essere utilizzato per utilizzare la terapia endocrina in donne con cancro invasivo alla mammella

POPULATION:	donne con cancro della mammella invasivo
INTERVENTION:	una soglia del 10% o più
COMPARISON:	1% o più cellule positive per il recettore degli estrogeni
MAIN OUTCOMES:	Overall survival; disease free survival; risposta diretta alla terapia endocrina (definita in accordo con WHO come risposta completa, parziale, nessun cambimanto, malattia progressiva); effetti avversi della terapia endocrina, e health-related quality of life.
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	<p>Lo stato dei recettori degli estrogeni (ER) e del progesterone (PR) di un carcinoma mammario invasivo fornisce informazioni sulla probabile risposta del tumore alla terapia endocrina. L'80% dei carcinomi mammari invasivi sono positivi ai recettori ormonali. La maggior parte dei tumori mammari positivi ai recettori ormonali sono positivi per gli ER. Una piccola percentuale di tumori negativi per gli ER è positiva per i PR e potrebbe beneficiare della terapia endocrina, ma c'è incertezza sui benefici della terapia endocrina in questi pazienti e se questa risposta dipende dal livello di positività dei PR.</p> <p>Tutti i carcinomi mammari invasivi vengono testati per lo stato degli ER come standard di cura. Molti centri/paesi testano i tumori anche per lo stato dei PR come pratica di routine. Alcuni centri testano solo i tumori negativi per gli ER per lo stato dei PR.</p> <p>Il metodo ottimale per il test del tumore per lo stato del recettore degli ormoni è l'immunoistochimica su tessuto fissato in formalina e incluso in paraffina usando anticorpi monoclonali. Gli studi sugli ER e PR vengono di solito eseguiti sul campione di biopsia, il che facilita la pianificazione precoce del trattamento, in particolare l'identificazione dei pazienti che potrebbero essere candidati alla terapia neoadiuvante. Gli studi sugli ER e PR possono essere ripetuti sul campione di escissione operatoria e c'è una forte correlazione con i risultati ottenuti sulla biopsia a core.</p> <p>Si raccomanda di effettuare il test sugli ER e PR secondo un protocollo di test di qualità garantita che rispetti le procedure di validazione del test e di assicurazione della qualità interne ed esterne.</p> <p>Storicamente sono stati utilizzati diversi metodi di valutazione dello stato degli ER e dei PR, inclusa la valutazione dell'intensità della percentuale di positività delle cellule tumorali nella colorazione dell'immunoistochimica.</p> <p>I livelli di soglia della colorazione dell'immunoistochimica, applicati per la categorizzazione di un tumore come positivo per il recettore ormonale, sono cambiati dal 10% al 5% all'1% al momento attuale. Pertanto, i pazienti con tumori mammari che mostrano una colorazione IHC positiva per gli ER e/o i PR in almeno l'1% delle cellule tumorali sono considerati probabili candidati per la terapia endocrina. Tuttavia, l'immunoistochimica si è evoluta negli ultimi decenni. I metodi di recupero stabiliti, gli anticorpi e i sistemi di rilevamento hanno aumentato la sensibilità dell'immunoistochimica.</p>
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	<b>Conditional recommendation against the intervention</b> ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	---	---	--	---

## CONCLUSIONI

Original

### Recommendation

In women with invasive breast cancer, the ECIBC Guidelines Development Group suggests administration of adjuvant endocrine therapy if 1% or greater of tumour cells show oestrogen receptor positivity rather than applying a threshold of 10% tumour cell oestrogen receptor positivity (conditional recommendation, very low certainty in the evidence).

### Justification

#### Overall justification

The GDG agreed by consensus that the limited very low quality evidence reviewed favours the current practice, using an oestrogen receptor (ER) threshold of 1% positivity.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable anticipated effects of a change in ER positivity threshold from current practice of 1% to 10% were trivial.

##### *Undesirable Effects*

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding thresholds, and the potential that patients with ER positivity between 1 and 10% would not be treated with the endocrine therapy.

##### *Certainty of evidence*

The GDG notes that the data included was very indirect and very low quality. Furthermore, it notes that interpretation of ER positivity thresholds based on data from the Honma study is limited due to the method of statistical analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each level of positivity.

Adolpment

### Recommendation

Nelle donne con cancro della mammella invasivo, il pane suggerisce la somministrazione di terapia endocrina adiuvante se l'1% o più delle cellule tumorali mostra positività agli estrogeni, rispetto ad utilizzare il 10% come criterio (raccomandazione su condizione, certezza molto bassa nelle evidenze)

### Justification

#### Overall justification

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable anticipated effects of a change in ER positivity threshold from current practice of 1% to 10% were trivial.

##### *Undesirable Effects*

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding thresholds, and the potential that patients with ER positivity between 1 and 10% would not be treated with the endocrine therapy.

##### *Certainty of evidence*

The GDG notes that the data included was very indirect and very low quality. Furthermore, it notes that interpretation of ER positivity thresholds based on data from the Honma study is limited due to the method of statistical analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each level of positivity.

### Subgroup considerations

Original

None were considered by the GDG.

Adolpment

Nessuna



## Implementation considerations

Original

The comparison is already current practice, therefore no implementation considerations were identified.

Adolopment

Nessuna

## Monitoring and evaluation

Original

The GDG suggests monitoring low (1-9%) and high (10% and above) ER positivity in relation to patient outcomes to better assess ER thresholds for treatment.

Adolopment

Nessuna

## Research priorities

Original

1. New research using ideally modern ER immunohistochemical techniques on tumor tissue primarily fixed in 10% neutral buffered formalin .
2. The GDG suggests additional observational studies to provide evidence on the current threshold used in practice, ideally using modern immunohistochemical techniques.

Adolopment

Nessuna

## REFERENCES SUMMARY

1. Nofech-Mozes S, Vella ET, Dhesy-Thind S, Hanna WM. Cancer care Ontario guideline recommendations for hormone receptor testing in breast cancer. *Clin Oncol (R Coll Radiol)*; 2012.
2. Rhodes, A. Frequency of oestrogen and progesterone receptor positivity by immunohistochemical analysis in 7016 breast carcinomas: correlation with patient age, assay sensitivity, threshold value, and mammographic screening. *J Clin Pathol*; 2000.
3. Harvey, J. M., Clark, G. M., Osborne, C. K., & Allred, D. C.. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol*; 1999.
4. Mohsin, SK. Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: a validation study. *Mod Pathol*; 2004.
5. Nofech-Mozes, S. Systematic review on hormone receptor testing in breast cancer. *Appl Immunohistochem Mol Morphol*; 2012.
6. Ellis IO, Al-Sam S, Anderson N, Carder P, Deb R, Girling A, Hales S, Hanby A, Ibrahim M, Lee AHS, Liebmann R, Mallon E, Pinder SE, Provenzano E, Quinn C, Rakha E, Rowlands D, Stephenson T, Wells CA. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. Cancer datasets and tissue pathways. Royal College of Pathologists UK.; 2016.
7. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC, Oncology, American Society of Clinical, Pathologists., College of American. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*; 2010.

## QUESITO 15

### Dovrebbe una soglia del 10% o più vs 1% o più cellule positive per il recettore del progesterone essere utilizzato per utilizzare la terapia endocrina in donne con cancro invasivo alla mammella

POPULATION:	donne con cancro della mammella invasivo
INTERVENTION:	una soglia del 10% o più
COMPARISON:	1% o più cellule positive per il recettore del progesterone
MAIN OUTCOMES:	Overall survival; disease free survival; risposta diretta alla terapia endocrina (definita in accordo con WHO come risposta completa, parziale, nessun cambimanto, malattia progressiva); effetti avversi della terapia endocrina, e health-related quality of life.
SETTING:	Italia
PERSPECTIVE:	Popolazione (Servizio Sanitario Nazionale)
BACKGROUND:	<p>Lo stato dei recettori degli estrogeni (ER) e del progesterone (PR) di un carcinoma mammario invasivo fornisce informazioni sulla probabile risposta del tumore alla terapia endocrina. L'80% dei carcinomi mammari invasivi sono positivi ai recettori ormonali. La maggior parte dei tumori mammari positivi ai recettori ormonali sono positivi per gli ER. Una piccola percentuale di tumori negativi per gli ER è positiva per i PR e potrebbe beneficiare della terapia endocrina, ma c'è incertezza sui benefici della terapia endocrina in questi pazienti e se questa risposta dipende dal livello di positività dei PR.</p> <p>Tutti i carcinomi mammari invasivi vengono testati per lo stato degli ER come standard di cura. Molti centri/paesi testano i tumori anche per lo stato dei PR come pratica di routine. Alcuni centri testano solo i tumori negativi per gli ER per lo stato dei PR.</p> <p>Il metodo ottimale per il test del tumore per lo stato del recettore degli ormoni è l'immunoistochimica su tessuto fissato in formalina e incluso in paraffina usando anticorpi monoclonali. Gli studi sugli ER e PR vengono di solito eseguiti sul campione di biopsia, il che facilita la pianificazione precoce del trattamento, in particolare l'identificazione dei pazienti che potrebbero essere candidati alla terapia neoadiuvante. Gli studi sugli ER e PR possono essere ripetuti sul campione di escissione operatoria e c'è una forte correlazione con i risultati ottenuti sulla biopsia a core.</p> <p>Si raccomanda di effettuare il test sugli ER e PR secondo un protocollo di test di qualità garantita che rispetti le procedure di validazione del test e di assicurazione della qualità interne ed esterne.</p> <p>Storicamente sono stati utilizzati diversi metodi di valutazione dello stato degli ER e dei PR, inclusa la valutazione dell'intensità e della percentuale di positività delle cellule tumorali nella colorazione dell'immunoistochimica.</p> <p>I livelli di soglia della colorazione dell'immunoistochimica, applicati per la categorizzazione di un tumore come positivo per il recettore ormonale, sono cambiati dal 10% al 5% all'1% al momento attuale. Pertanto, i pazienti con tumori mammari che mostrano una colorazione IHC positiva per gli ER e/o i PR in almeno l'1% delle cellule tumorali sono considerati probabili candidati per la terapia endocrina. Tuttavia, l'immunoistochimica si è evoluta negli ultimi decenni. I metodi di recupero stabiliti, gli anticorpi e i sistemi di rilevamento hanno aumentato la sensibilità dell'immunoistochimica.</p>
CONFLICT OF INTEREST:	<u>Gestione del conflitto di interesse (Col)</u> : Le dichiarazioni di interesse di tutti i membri del panel sono state valutate dal CTS e gestite dall'ONS seguendo la procedura adottata per il Sistema Nazionale Linee Guida. Per nessun membro del panel è stata inibita la partecipazione allo sviluppo delle raccomandazioni o alla votazione della raccomandazione.

## TIPO DI RACCOMANDAZIONE

Strong recommendation against the intervention ○	<b>Conditional recommendation against the intervention</b> ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	---	---	--	---

## CONCLUSIONI

Original

### Recommendation

In women with invasive breast cancer, the ECIBC Guidelines Development Group suggests administration of adjuvant endocrine therapy if 1% or greater of tumour cells show progesterone receptor positivity rather than applying a threshold of 10% tumour cell progesterone receptor positivity (conditional recommendation, very low certainty in the evidence).

### Justification

#### Overall justification

The GDG agreed by consensus that the limited, very low quality evidence reviewed, favours the current practice, of using a progesterone (PR) threshold of 1% positivity.

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable anticipated effects of a change in PR positivity thresholds, from the current practice of 1% to a 10%, were trivial.

##### *Undesirable Effects*

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding the thresholds, and that, potentially, patients with PR positivity between 1 and 10% would not be treated with the endocrine therapy.

##### *Certainty of evidence*

The GDG notes that the data included was very indirect and of very low quality. Furthermore, it notes that interpretation of PR positivity thresholds based on data from the Honma study is limited due to the statistical method analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each positivity level.

Adolopment

### Recommendation

Nelle donne con cancro della mammella invasivo, il panel suggerisce la somministrazione di terapia endocrina adiuvante se l'1% o più delle cellule tumorali mostra positività al recettore del progesterone, rispetto ad utilizzare il 10% come criterio (raccomandazione su condizione, certezza molto bassa nelle evidenze)

### Justification

#### Overall justification

#### Detailed justification

##### *Desirable Effects*

The GDG judged that the desirable anticipated effects of a change in PR positivity thresholds, from the current practice of 1% to a 10%, were trivial.

##### *Undesirable Effects*

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding the thresholds, and that, potentially, patients with PR positivity between 1 and 10% would not be treated with the endocrine therapy.

##### *Certainty of evidence*

The GDG notes that the data included was very indirect and of very low quality. Furthermore, it notes that interpretation of PR positivity thresholds based on data from the Honma study is limited due to the statistical method analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each positivity level.

## Subgroup considerations

Original

None were considered by the GDG.

Adolopment

Nessuna

## Implementation considerations

Original

The comparison, using a threshold of 1%, is already current practice, therefore no implementation considerations were identified.

Adolopment

Nessuna

## Monitoring and evaluation

Original

The GDG suggests monitoring low (1-9%) and high (10% and above) PR positivity in relation to patient outcomes to better assess PR thresholds for treatment.

Adolopment

Nessuna

## Research priorities

Original

1. New research using ideally modern PR immunohistochemical techniques on tumor tissue primarily fixed in 10% neutral buffered formalin.
2. The GDG suggests additional observational studies to provide evidence on the current threshold used in practice, ideally using modern immunohistochemical techniques.

Adolopment

## REFERENCES SUMMARY

1. Nofech-Mozes S, Vella ET, Dhesy-Thind S, Hanna WM.. Cancer care Ontario guideline recommendations for hormone receptor testing in breast cancer. Clin Oncol (R Coll Radiol); 2012.
2. Rhodes, A. Frequency of oestrogen and progesterone receptor positivity by immunohistochemical analysis in 7016 breast carcinomas: correlation with patient age, assay sensitivity, threshold value, and mammographic screening. J Clin Pathol; 2000.
3. Harvey, J. M., Clark, G. M., Osborne, C. K., & Allred, D. C.. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol; 1999.
4. Mohsin, SK. Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: a validation study. Mod Pathol; 2004.
5. Nofech-Mozes, S. Systematic review on hormone receptor testing in breast cancer. Appl Immunohistochem Mol Morphol; 2012.
6. Ellis IO, Al-Sam S, Anderson N, Carder P, Deb R, Girling A, Hales S, Hanby A, Ibrahim M, Lee AHS, Liebmann R, Mallon E, Pinder SE, Provenzano E, Quinn C, Rakha E, Rowlands D, Stephenson T, Wells CA.. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. Cancer datasets and tissue pathways. Royal College of Pathologists UK.; 2016.
7. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC, Oncology, American Society of Clinical Pathologists., College of American. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol; 2010.

Sezione	Commento esterno	Letteratura a supporto	Revisore esterno	Risposta
Osservazioni generali	Come riconosciuto dagli autori, un possibile limite dell'approccio delle linee guida "per PICO" è rappresentato dalla loro veste finale, che risulta apparentemente frammentaria. Fatta salva l'auspicabilità di un vero e proprio PDTA nazionale		Lucioni	Osservazione accettata. E' stata aggiunta un'ulteriore sinossi in introduzione al documento

	per la prevenzione e la diagnosi del carcinoma mammario, la fruibilità del documento potrebbe forse giovare, in aggiunta alla sinossi iniziale delle raccomandazioni, di una breve introduzione che illustri le raccomandazioni scelte e le evidenze che hanno determinato la loro adozione/adolopment.			
<b>Osservazioni generali</b>	[Pagina 10 Introduzione e rationale]: “Il panel ha deliberato 15 raccomandazioni: 11 discusse per esteso e 2 determinate logicamente sulla base delle altre raccomandazioni.” Mi pare che manchino due raccomandazioni (11+2 = 13).		Lucioni	L’errore è stato corretto
<b>Osservazioni generali</b>	[Pagina 49, riga 3 e 5]: Correggere “did not included” con “did not include”		Lucioni	L’errore è stato corretto
	[Pagina 66, riga 1]: “Other histopathology tests ...” è scritto due volte.		Lucioni	L’errore è stato corretto
<b>Osservazioni generali</b>	[Pagina 142 paragrafo recommendation, riga 3]: correggere “utilisso” con “utilizzo”		Lucioni	L’errore è stato corretto
<b>Osservazioni generali</b>	[Pag. 161, paragrafo background]: “Storicamente sono stati utilizzati diversi metodi di valutazione dello stato degli ER e dei PR, inclusa la valutazione della forza e della percentuale di positività delle cellule tumorali nella colorazione dell’immunoistochimica”.		Lucioni	Osservazione accettata.

	Suggerirei di sostituire la parola “forza” con “intensità”			
<b>Osservazioni generali</b>	[Pag 164, paragrafo background]: “Storicamente sono stati utilizzati diversi metodi di valutazione dello stato degli ER e dei PR, inclusa la valutazione della forza e della percentuale di positività delle cellule tumorali nella colorazione dell'immunoistochimica”. Suggerirei di sostituire la parola “forza” con “intensità”		Lucioni	Osservazione accettata.
<b>Sinossi raccomandazioni</b>	<b>Raccomandazione quesito 5:</b> [in riferimento alla core biopsy] Credo che si intenda sempre la "vacuum assisted biopsy" e non la core needle biopsy che invece utilizza l'ago tranciante senza sistema di vuoto. Al di là della guida utilizzata se sono confidente di vedere le calcificazioni sotto guida ecografica, la vacuum assisted biopsy è adeguata ed appropriata anche senza guida mammografica.		Trimboli	Nelle raccomandazioni Europee si fa riferimento alla guida, indipendentemente dal tipo di biopsia utilizzato (vacuum assisted o core biopsy con ago tranciante). La raccomandazione è stata adottata nella sua formulazione originale.
<b>Quesito 1</b>	La letteratura considerata fino al 2010-2015 è gravata da bias metodologici come argomentato nei vari punti del giudizio. La letteratura più recente include studi osservazionali e randomizzati (in particolare sui CDIS) che mostrano che gli effetti desiderabili potrebbero superare quelli indesiderabili in	<ul style="list-style-type: none"> <li>Balleyguier C, Dunant A, Ceugnart L et al. Preoperative Breast Magnetic Resonance Imaging in Women With Local Ductal Carcinoma in Situ to Optimize Surgical Outcomes: Results From the Randomized Phase III Trial IRCIS. J Clin Oncol. 2019 Apr 10;37(11):885-892. doi: 10.1200/JCO.18.00595.</li> </ul>	Trimboli	Osservazione accettata. Sono state integrate le referenze e una nota è stata aggiunta nell'EtD

	<p>popolazioni selezionate. La RM non aumenta le mastectomie garantendo la conferma della chirurgia conservativa nella maggior parte dei casi e riducendo i re-interventi per margini positivi. Condizione necessaria per la valutazione degli outcome negli studi dedicati è la gestione dei reperti addizionali riscontrati alla RM con verifica istologica nel caso in cui impattino sul trattamento e la comunicazione di tali risultati alla chirurgia.</p> <p><b>Research priorities.</b> Ulteriori studi ben condotti sono cruciali nel CDIS di grado 3 come precursore del carcinoma invasivo. La RM ha un vantaggio di sensibilità e di accuratezza del parametro T che bisogna capire se si riflette su una chirurgia più radicale con minori margini positivi e recidive nell’ottica di prevenzione primaria della malattia infiltrante.</p>	<ul style="list-style-type: none"> <li>▪ Lehman CD, Gatsonis C, Romano J et al. Association of Magnetic Resonance Imaging and a 12-Gene Expression Assay With Breast Ductal Carcinoma In Situ Treatment. <i>JAMA Oncol.</i> 2019 Jul 1;5(7):1036-1042. doi: 10.1001/jamaoncol.2018.6269.</li> <li>▪ Yoon GY, Choi WJ, Kim HH, Cha JH, Shin HJ, Chae EY. Surgical Outcomes for Ductal Carcinoma in Situ: Impact of Preoperative MRI. <i>Radiology.</i> 2020 May;295(2):296-303. doi: 10.1148/radiol.2020191535.</li> <li>▪ 4. Sardanelli F, Trimboli RM, Houssami N et al. Magnetic resonance imaging before breast cancer surgery: results of an observational multicenter international prospective analysis (MIPA). <i>Eur Radiol.</i> 2022 Mar;32(3):1611-1623. doi: 10.1007/s00330-021-08240-x.</li> </ul>		
<b>Quesito 1</b>	Nell’allegato viene dettagliato l’utilizzo di diverse tecniche nell’ambito della stadiazione preoperatoria del tumore della mammella.	<ul style="list-style-type: none"> <li>▪ [Allegato]: Raccomandazioni diagnosi preoperatoria lesioni mammarie – GIPaM (Gruppo Italiano Patologi della Mammella).</li> </ul>	Rizzo	Osservazione accettata.
<b>Quesito 2</b>	Subgroup considerations Studi recenti mostrano che la CEM è alternativa valida alla RM	<ul style="list-style-type: none"> <li>▪ Hogan MP, Amir T, Mango VL, Morris EA, Jochelson MS. Feasibility of contrast-enhanced</li> </ul>	Trimboli	Osservazione accettata. Una nota è stata aggiunta nell’EtD



	<p>anche nei carcinomi lobulari (Lobbes M, in press) e nelle pazienti con protesi.</p> <p>Per quanto riguarda lo studio del burden linfonodale, la RM non è la metodica di scelta pertanto la CEM anche in questo caso non è inferiore alla RM.</p>	<p>mammography in women with breast implants. Clin Imaging. 2023 Jan; 93:31-33. doi: 10.1016/j.clinimag.2022.10.012. Epub 2022 Oct 27.</p>		
<b>Quesito 4</b>	<p>Il quesito 4 (agobiopsia mammaria vs citologia da agoaspirato con ago sottile per la diagnosi di carcinoma mammario in donne con lesioni sospette alla mammografia) promuove (a ragione) una raccomandazione forte a favore dell'approccio agobiottico. A tale riguardo la situazione italiana presenta un certo grado di disomogeneità nella prassi, che risulta non sempre congruente con la raccomandazione. Il panel suggerisce l'opportunità di monitorare l'applicazione di tale raccomandazione sul territorio italiano attraverso l'identificazione di indicatori ad hoc. Si suggerisce l'opportunità di approfondire questo punto, precisando i possibili indicatori da valutare e definendo criteri che consentano una piena adesione alla raccomandazione.</p>	-	Lucioni	<p>Abbiamo aggiunto nel monitoraggio la definizione dell'indicatore proposto: proporzione di approfondimenti con FNAC sul totale di approfondimenti con prelievo di tessuto (FNAC+CNB+VABB). Abbiamo anche aggiunto l'indicatore: proporzione di casi operati con solo accertamento citologico pre-operatorio.</p>
<b>Quesito 4</b>	<p>Aggiungerei che il profilo molecolare ottenuto sulla core needle biopsy rappresenta ad oggi il gate keeper su lesioni</p>		Trimboli	<p>Osservazione accettata. Una nota è stata aggiunta nell'EtD</p>

	tumorali anche di un cm (HER2 enriched e tripli negativi).			
<b>Quesito 5</b>	<p>Il quesito 5 (VABB a guida stereotassica vs VABB ecoguidata per diagnostica il carcinoma mammario in donne positive per calcificazioni al seno) favorisce l'utilizzo di VABB a guida stereotassica. Un ostacolo alla corretta applicazione di questa raccomandazione nella pratica clinica, come indicato dagli autori, potrebbe verificarsi in quei contesti nei quali l'equipaggiamento stereotattico non è ampiamente disponibile. In queste situazioni dovrebbe essere necessariamente previsto un percorso che consenta alle pazienti con microcalcificazioni di accedere alla procedura diagnostica più indicata. Potrebbe inoltre essere utile definire più in dettaglio i sottogruppi di calcificazioni (associate o no a massa, o a distorsioni, tipologia di calcificazioni etc) per le quali la biopsia ecoguidata potrebbe essere accettabile.</p>	-	Lucioni	<p>La popolazione di riferimento per questa raccomandazione sono donne in cui il sospetto diagnostico nella mammografia è motivato dalle calcificazioni e l'oggetto dell'approfondimento istologico è il tessuto che presenta le calcificazioni. Nel caso di calcificazioni associate a masse o a distorsioni parenchimali per le quali il tessuto che si intende prelevare è quello associato alla massa o alla distorsione, la raccomandazione potrebbe non applicarsi.</p>
<b>Quesito 5</b>	<p>La sostanziale differenza nell'approfondimento istologico delle microcalcificazioni sta nel sistema di biopsia, non tanto nella guida. Si raccomanda di utilizzare la vacuum assisted biopsy (VAB appunto) invece</p>		Trimboli	<p>Vedi sopra. Nelle considerazioni per l'implementazione è stato inserito il commento che in Italia la biopsia a guida stereotassica è più spesso associata a VABB.</p>

	<p>delle core needle biopsy (CNB) che usa un ago tranciante senza sistema di vuoto.</p> <p>Non credo che in italia si utilizzi la core needle biopsy sotto guida stereotassica.</p> <p>Al di là della guida utilizzata, se stereotassica o ecografica, se sono confidente di vedere le calcificazioni sotto guida ecografica, la vacuum assisted biopsy è adeguata ed appropriata anche senza guida mammografica.</p>			<p>È stata aggiunta una nota nelle considerazioni aggiuntive in cui si riporta che il rischio di non campionare la lesione è minore con la VABB a prescindere dalla guida utilizzata.</p>
<b>Quesito 6</b>	<p>L'acronimo corretto è VABB (vacuum assisted breast biopsy) non VANCB (needle core biopsy per definizione non è vacuum assisted)</p>		Trimboli	<p>La raccomandazione si riferisce alla VANCB (vacuum assisted needle core biopsy), come da raccomandazione originale dell'European Commission Initiative on Breast Cancer</p>
<b>Quesito 6</b>	<p>Non è chiaro se il quesito si riferisca a tutte le pazienti o esclusivamente alle pazienti con microcalcificazioni o alle pazienti candidate a NAT.</p> <p>Non mi risulta che nella pratica quotidiana si localizzino mediante clip tutte le lesioni non palpabili (masse o distorsioni) sottoposte a CNB sotto guida ecografica.</p> <p>Nel caso delle microcalcificazioni sottoposte a VAB si procede sempre al posizionamento della clip nel letto della biopsia anche per la frequente mancanza di calcificazioni residue dovuto</p>		Trimboli	<p>La raccomandazione si riferisce a tutte le donne, vedere le subgroup considerations per il chiarimento sulla non distinzione tra lesioni palpabili e non palpabili</p>

	all'utilizzo di aghi di grosso calibro.			
<b>Quesito 12/13</b>	<p>Le raccomandazioni 12 e 13 non sono molto chiare. Sembrano incongruenti.</p> <p>Il Panel sostiene che non ci sia vantaggio dell'imaging convenzionale se si utilizza la PET nelle pazienti in stadio III senza sintomi di metastasi ma raccomanda di eseguire una PET dopo imaging convenzionale. Chiederei di chiarire questo passaggio.</p>		Trimboli	<p>Nessuna delle due raccomandazioni si esprime rispetto all'utilizzo dell'imaging convenzionale, in quanto la raccomandazione 12 raccomanda la PET vs. no PET e la 13 raccomanda PET + imaging vs. imaging da solo</p>