EUROPEAN High Resolution Study

Errata and Clarifications

August 10, 2014

Errata and Clarifications for the protocol of the European High Resolution (HR) Study are included in this document.
The first version of the study protocol was sent to the European population based Cancer Registries in December 2013. After the protocol was circulated and shared among the European participants, some ambiguities/inaccuracies were identified and some clarifications appeared necessary. The present document clarifies all reported doubts and the new version of the list of variables to be collected (versions 2.0-2.3 – for both a .txt and access data collection).
Please note that only two optional variables were been identified as incorrect.
In few days, an electronic version of the corrected and updated list of variables will be available on the EUROCARE website.
If there are any questions about the document or in case additional doubts/inaccuracies are identified, please notify this to the **HR helpdesk**:
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In the following pages the reported doubts (or inaccuracies) are listed and the relevant clarifications (or changes) are listed, along the list of variables that was originally shared:

0. General notes

0.1 Variable numbering

In the list of variables to be collected, the identification number "14" was related to both "grading" and "basis of diagnosis".

R: "Basis of diagnosis" is now re-enumerated as 15 and the site-specific variables numbering was changed accordingly. Here, the correct sequence numbers for the site-specific variables range:

- Breast cancer: 57 to 140
- Colorectal cancer: 57 to 113
- Lung cancer: 57 to 101
- Skin melanoma: 57 to 111
- Lymphoma: 57 to 125

0.2 TNM Stage

Why are there both X and 9 (Not available) codes in the same variable? Isn't it the same?

R: The X code means that the register found the clinical records and yet the specific information was not included. The "9 (Not available)" code means that the clinical documentation is not available.
In the final analyses, however, the X and "9 (Not available)" codes will likely be grouped.

0.3 T stage

Shouldn't "Tis" be only possible for the breast cancer study (only site allowing for in situ tumours)?

R: During the 2nd HR Workshop in Ispra, in September 2013, it was decided to collect only the in situ breast cancers. However, to keep consistency with the TNM staging classification, all the envisaged categories are taken into consideration.

0.4 N stage (both clinical and pathological)

It is not clear what the N+NAS category/option means and how to use it.

R: We apologise: this is a typo error. "NAS" should be intended as "Not Otherwise Specified": the category is now named "N+NOS", along with the English translation.
Sometimes, it could happen that the information on N stage is not highly detailed in the clinical notes. In these cases, it is possible to only report the involvement of regional lymph nodes. You can also use the category/option "N+" to collect the information on N stage.

0.5 M stage

Q1: In case of metastatic tumour at diagnosis, it could be interesting to include and collect the information on the site of metastasis.

R: We agree. Information on the site of metastasis is very detailed and was only introduced within the colorectal cancers parallel group. For the other tumours, we propose to introduce the optional collection of this new variable.

Q2: What time-interval should we consider for recording positive cM and pM? For example: if a metastasectomy occurs 3 or 6 months (or more) after surgery, what would be the cut point to define cM and pM as positive? (e.g. 3 months, 6 months or longer?)

R: In general, we consider clinical or pathological M1 if M1 stage is established within 6 months since diagnosis. After this period, we consider it as "relapse".

0.6 Treatment for the cancer under study

What should we consider as time-interval between the diagnosis of the solid tumours and its treatment? (e.g. one year, two years, other?)

R: We identify 6 months to be the time-interval between the diagnosis of the solid tumour and its FIRST treatment. These, however, are general indications, as longer time intervals could occur and should be established case by case. For example, a patient may postpone cancer primary treatment due to co-morbidities.

0.7 Diagnostic exams for distant metastases

Should every possible imaging modality (RX, CT, PET, bone scintigraphy, ultrasound, …) be counted in?

R: Yes, as in the Annexes A/B, each imaging modality has to be considered.

Below, each variable is identified with the NEW number, taking into consideration the above mentioned re-enumeration and some new optional or compulsory variables added from the initial protocol (as requested by some of European colleagues –details below -).

1. Notes on common variables

1.1 Variables 2-3: Identification code, tumour identification code

Is it possible to have the same number for variable 2 and 3? (or does variable 2 refer to the patient and variable 3 to the tumour?)

R: These two variables are the same as those collected for the general EUROCARE study, thus in variable 3 (tumour identification code) the unique tumour identification code used by the cancer registry for each tumour registered in its database has to be included. Together with person code (variable 2, identification code), this code will enable to distinguish in the analyses multiple primary tumours in the same person.

However, it is possible to have the same number for the two variables, because variable 3 (tumour identification code) is not a compulsory variable, as not all cancer registries use it.

The distinction of these two variables is important for breast cancer, for which two different records have to be filled in case of bilateral tumours. See the breast cancer-specific part for more details.

1.2 Variables 5-10: Date of birth, date of incidence

Should we exclude the case in case of missing information?

R: In case of missing information on age at diagnosis and date of incidence, the record will be excluded.

1.3 Variable 14: Grading

According to the ICD-O-3 classification, the unknown grading should be 9 instead of 8. We suggest changing this code, since it may lead to some misclassification, especially for lymphoma, since there is a specified code 8 in ICD-O-3 for these tumours.

R: According to the ICD-O-3 classification, we have now modified the categories/options. However, please consider that in the present study only Follicular and Diffuse Large B-cell lymphomas are included.

1.4 Variable 19: Multidisciplinary team consulting meeting

Does this refer to decisions taken at the date of diagnosis/ after or before the date of diagnosis/ at the time the treatment (neo-adjuvant, adjuvant, palliative) or relapse took place?

R: This variable was deeply discussed during the HR workshops held Ispra in 2013. As a conclusion, it was decided to report whether the decision of the multidisciplinary team was present in the clinical records.

1.5 Variables 20-39: Charlson index (optional) and related items

Q1: If this index is not available in the clinical notes, should we score it using items 21-39?

Q2: If this index is not available in the clinical notes, how do we calculate it? This is not mentioned in Annex C.

R: It's not necessary to score this if not available in the clinical notes. The most important thing is to indicate the presence or absence of each item for co-morbidities.

However, if you would like to calculate the Charlson index score, you will add up the scores (1, 2, or 6 indicated in the third column of Annexes A/B) only if the analysed co-morbidity is present (See the Charlson index definition now in Annex C).

If you have a pre-recorded co-morbidity index, please describe how it was calculated.

Q3: In the medical files there never is information that a patient does not have a certain condition, it only mentions which conditions the patient actually has. In this situation, could we code the co-morbidities that are not mentioned in the medical files as "2=no"? In practical terms, this is what the clinicians assume when treating the patients.

R: We agree with recording "2=no" if the co-morbidity is not mentioned in the clinical notes.

Q4: How should we code "Lymphoma" as co-morbidity in the lymphoma HR study? Should we code "1=yes" if there is an additional lymphoma not included in the present study (i.e. not a FL or DLBCL) or "2=no otherwise"?

R: If the clinical notes include the diagnosis of another lymphoma (different from FL or DLBCL), please record as "1=yes".

Q5: How should we code "Diabete without end organ damage" and "Diabete with end organ damage" if in the clinical files there is no information on "end organ damage"?
R: To be consistent with the above coding of Q3, this should be coded as "Diabetes without end organ damage".

Q6: If a patient has hemiplegia (variable 31=yes), should we code variable 24 (cerebrovascular disease) =yes as well?
R: No, because the hemiplegia is a condition that is not necessarily due to cerebrovascular disease.

Q7: In the protocol, there is no variable for hypertension. Is it ignored or should we use some other variable?
R: The main reason is that hypertension is not included in the Charlson index list. During the HR workshop held in 2013, we decided to exclude hypertension in this study protocol.

Q8: It is not clear whether to collect information on co-morbidities occurring at the date of diagnosis (with active disease at the time of diagnosis) or disease that have occurred long before the diagnosis was made. What cut point for time interval between the co-morbidity and the diagnosis of the cancer should we consider? For example: if myocardial infarction occurred 5 years before the cancer diagnosis, would we record this as co-morbidity?
R: As reported in the lists of variable to be collected (Annexes A/B) the information on co-morbidities should be referred to the date of diagnosis (with active disease). This is very important because on the basis of the presence of any co-morbidity, the cancer treatment could be modified. However, as reported in the SEER-Medicare presentation *(http://appliedresearch.cancer.gov/seermedicare/training2013/Segment%2012-Comorbidity%20and%20Risk-April%202013.pdf)*, you have to exclude the month of diagnosis and count back 12 months. Thus, Charlson co-morbidity index may refer up to the last 12 months before cancer diagnosis.

1.6 Variable 41: Body Mass Index (BMI)

For the majority of cases this information is not collected at the time of diagnosis. However, for some cases BMI may be derived from the medical records at the beginning of the treatment. Is it recommendable to only collect this information when it refers to the diagnosis or should we also collect BMI, if available, at the time the treatment was initiated?
R: Although the information on co-morbidities should be referred to the date of diagnosis, it is well known that, in general, the BMI is necessary to understand what type of chemotherapy should be done. Thus, we think that ONLY for BMI, the value could be referred to the date of treatment.

1.7 Variables 42-43: Type of scale and score for performance status

Does this refer to the diagnosis or at to the beginning of the treatment, or even to both diagnosis and treatment?
R: As the same as the information on co-morbidity, the information on performance status refers to the date of diagnosis.

1.8 Variable 44: Relapse

Should we consider defining relapse the time the treatment finalized or from the date of diagnosis?
R: In general, we consider clinical or pathological M1 if M1 stage is established within 6 months since diagnosis. After this period, we consider it as "relapse".

1.9 Variables 17, 48: Multiple tumour, second cancer (or previous cancers)

Q1: In the database there is only the possibility to collect information of second primary events occurring after the first cancer event, but it is not possible to collect information on previous tumours occurring before this event. In other words, for multiple primaries it is only possible to record information on the first cancer and subsequent cancers, but not so for previous tumours.
Q2: As for multiple tumours diagnosed before the tumour under study, it is not possible to indicate the cancer site and the date of diagnosis. At the moment it is only possible to indicate the date of the subsequent tumour. Thus, if a previous tumour was diagnosed, have we to indicate it as presence of tumour in the list of co-morbidity?
R: Please, record the presence of the previous multiple cancers in the list of co-morbidity. During the HR meeting held in Ispra last year, there was a long discussion about this point and the majority of participants agreed on the fact that is better not to collect this detailed information, as it is not very important for the aims of the present study.

1.10 Variables 54-56: Date of last known contact

Is this the date of vital status/date of death?

R: Not necessarily. Some cancer registries do not conduct the linkage between the cancer registry database and the population database every year. For this reason, it is possible that the date of last contact corresponds to the date of last treatment or medical examination.

2. Notes on site-specific variables

2.1 Breast

2.1.1 Variables 2-3: Identification code, tumour identification code for bilateral tumours

Q1: In case of bilateral breast cancer, should we have two records with the same variable 2 (identification code) but different variable 3 (tumour identification code)?

Q2: If the cancer registry does not register bilateral breast cancer as new events (i.e. it registers them into the same localization to identify them), is it possible to use a sub-number or a sequential letter for variable 2 (identification code) - for example: 11-0311.a (i.e. for the left breast) and 11-0311.b (i.e. for the right breast) or 11-0311.1 (i.e. for the left breast) and 11-0311.2 (i.e. for the right breast) -?

R: In case of bilateral breast cancer, the same code in variable 2 (identification code) has to be maintained, but a different code in variable 3 (tumour identification code) has to be used.

Thus,

Left breast: Identification code=11-0311 ; tumour identification code= 11-0311.a
Right breast: Identification code=11-0311 ; tumour identification code= 11-0311.b

Q3: Do you confirm that we have to register two different records for synchronous bilateral tumours?

R: Yes.

Q4: In the case of a woman with synchronous events as a tumour /2 (in situ) and another tumour /3 (invasive). Do we have to record both?

R: According to ENCR rules the two lesions are distinct, please record two tumours: one invasive and the other in situ. Otherwise, please make sure that it is really a multiple and not a multifocal tumour.

2.1.2 Variable 58: Modality of diagnosis

Q1: It might be confusing to stratify detection mode only in screened-detected and symptomatic tumour. Should opportunistic screening be included in screened-detected cancers? Some cancers are not symptomatic but neither detected in a screening program. Furthermore, it should be highly interesting to know if a case is an interval cancer, which are symptomatic but from women participating in a screening program.

Q2: I supposed it was complicated to have information on screening programs. Some registries consider opportunistic screening as symptomatic (as you often do not know that they are opportunistic screening) and others would consider them as screened-detected. So, perhaps opportunistic screening should be considered as screened-detected and interval cancers should be considered as symptomatic. Thus, analyzes according to symptomatic/non-symptomatic cancers would be performed.

Q3: Does the "screened-detected" option refer to an established screening program only or could this also be a laboratory or gynaecological examination?

R: The "screened-detected" category indicates either opportunistic or organized screening. Thus, the aim of this variable is to distinguish between symptomatic and asymptomatic cancers. This study design is not appropriate to evaluate the screening programs (case interval, symptoms, screening completeness).

2.1.3 Variable 66: Biopsy

Most of cases present the fine needle aspiration biopsy as diagnostic examination. Should we record biopsy as "not done"?

R: As in Annexes A/B, variable 66 also includes fine needle aspiration.

2.1.4 Variables 74-75, 78-79, 81-82, 83-84, 138-140: cTNM, pTNM, yTNM and total number of examined and positive nodes

Q1: Is it necessary to collect cTNM if ypTNM is available?

R: Yes, it is necessary and strongly recommended. The clinical TNM stage is very useful in case of neo-adjuvant treatment to understand the stage at diagnosis. In fact, as the main aim of this European HR study is to evaluate the adhesion to internationally agreed clinical guidelines, in the majority of cases the stage at diagnosis is requested.

Q2: If yTNM has to be registered, pTNM should be left blank or other coding is suggested (e.g. not proceed). And if the "neo-adjuvant" treatment was not performed, should yTNM be left blank or else…?
Q3: In case of neo-adjuvant therapy, should we code pT (variable 74) and ypT (variable 138) in the same way? The same question goes to the pair of variables pN (variable 78) and ypN (variable 139). And, how should we code the total number of examined (variable 81) and metastatic (variable 82) nodes?
R: If a neo-adjuvant treatment was performed, ypTNM (ypT, ypN, yM) should be recorded and the pTNM (pT, pN, M) should be left blank. If a neo-adjuvant treatment was not performed, pTNM (pT, pN, M) should be recorded and the ypTNM (ypT, ypN, yM) should be left blank.
As for the number of examined and positive lymph nodes, if a neo-adjuvant treatment was performed, these numbers should be collected in the dedicated variables (81, 82). For this reason, we modified the "note" in Annexes A/B.

2.1.5 Variables 74, 78, 83, 80, 81, 104: pTNM, total number of examined and positive nodes, and surgery

Q1: If a woman underwent lumpectomy/quadrantectomy with a certain pTNM followed by mastectomy with a new pTNM: which is the pTNM we should consider? What about the number of examined and of metastatic nodes?
Q2: In some cases it may happen that a woman undergoes a lumpectomy and later she undergoes a simple or radical mastectomy. Which is the one we should record: the lumpectomy or the simple/radical mastectomy?
R: In case of consecutive surgeries, the most extensive/radical surgery (in this example, the mastectomy) should be recorded as well as the related pTNM. As regards the number of examined and positive lymph nodes, they should be summed up.

2.1.6 Variable 80: Immunohistochemical determination of nodal micrometastases (optional).

Some cases have OSNA (One Step Nucleic Acid Amplification) instead. How should we proceed?
R: As we cannot collect all this detail, for the purposes of the present study this variable has been changed into "Determination of nodal micrometastases (optional)" including all possible methods (immunohistochemistry, OSNA, etc.). we have now included a specific note in Annexes A/B.

2.1.7 Variables 91, 94, 97, 102: ER, PR, Ki67 and HER2 percentage

Q1: We don't have the percentage, but an interval such as 75-100%. How should we code these variables?
R: We have now changed the variable from a pre-defined to a free-text variable. In this way, both single percentages and ranges can be recorded.

Q2: Should the percentage of HER2 cells be reported only if HER2 (variable 100) is not available?
Q3: Is the percentage value applicable to HER2?
R: In general, it is much more important to report the percentage of HER2 positive cells instead of the synthesised result. This is justified by the fact that if the cut-off for positivity changes over time, it is always possible to harmonise the synthesised categories with the new guidelines.

2.1.8 Variables 92, 95, 98, 100: ER, PR, Ki67 and HER2 positivity

The percentage of positive cells is not always known. However, it is known if the biomarker is positive/negative or high/low. In this case, sometimes the cut-off is also known, mainly for Ki67. Should it be included somewhere?
R: We know that this information is very useful but, presently, it is not possible to ask for all these variables as compulsory. We propose the optional collection of variables 93, 96, 99, 103.

2.1.9 Variable 100: HER2

We have cases with score 0 for Her2, but the options proposed are: not done; 1+; 2++; 3+++. How should we code it?
R: Thanks for this remark. We have now modified the categories/options for the immunohistochemical result for HER2 as follows:

0 = not done
1 = 0 (negative)
2 = 1+ (negative)
3 = 2++
4 = 3+++ (positive)
9 = unknown

2.1.10 Variable 102: FISH

Q1: Some hospitals might not use FISH but other hybridization assays, this might be commented. Furthermore, a variable for the FISH result is lacking (positive/negative/unknown). In order to know the HER2 status, the immunohistochemical result (variable 96) and the hybridization assay result would be needed.

Q2: How should we record "HER2=2+, Fish done and positive result" cases?

R: We know that some hospitals don't use FISH. In fact, in Annexes A/B, in "hormonal status", we wrote: "In general obtained by immunohistochemistry. If other methods were used, please specify in a separate document". As we cannot collect this detail, for the purposes of the present study the term "FISH" indicates the possible in situ hybridization assays for HER2 (e.g. FISH, SISH, CISH or other methods), which should be specified in a separate document.

However, we have now modified the categories/options for this variable, as follows:

0 = not done
1 = done, positive
2 = done, negative
3 = done, unknown result
9 = unknown

2.1.11 Variables 91-103: Hormonal status

Hormonal receptor status is usually performed at the biopsy but it could also be evaluated when the piece of lumpectomy/mastectomy is taken. The results often vary between these. Which is the status of interest?

R: The value obtained examining the largest piece should be recorded (e.g., if biopsy and mastectomy are performed, values on mastectomy are to be preferred).

2.1.12 Variables 104-137: Treatments for breast cancer

Although it is not so common, it could be interesting to collect the treatment, above all, surgery also for metastatic cases.

R: We agree. For this reason, we have now dropped the note on collecting all variables related to treatments only for M0 cases and we have now included the yM variable.

2.1.13 Variable 109: Surgical radicality

We do not understand the meaning. Please, give the definition.

R: Surgical radicality refers to the complete or incomplete removal of the tumour under study.

As reported in the TNM, 7th version (page 17), the absence or presence of residual tumour after treatment is described by the symbol R. The TNM and pTNM - describing the anatomical extent of cancer in general without considering treatment - can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. The definitions of the R categories are:

RX. Presence of residual tumour cannot be assessed
R0. No residual tumour
R1. Microscopic residual tumour
R2. Macroscopic residual tumour

As you can note, R0 is comparable to our old option 1 ("no residual tumour"), RX to our option 9 ("unknown"); whereas, R1 and R2 are both included in our option 2 ("presence of residual tumour").

It is important to underline that for some people the R classification is applicable only to the primary tumour for others it is applicable also to the distant metastases. In such study, we would like to **include** in this definition also the **distant metastases**: in the case of metastatic cancer at diagnosis, you have to select "no residual tumour" only if both the primary tumour and the distant metastasis were completely removed during surgery.

However, we have now modified the definition making it homogeneous with the TNM classification:

1 = R0, no residual tumour
2 = R1, microscopic residual tumour
3 = R2, macroscopic residual tumour
4 = R1/R2, presence of residual tumour but unknown if R1 or R2
9 = RX, presence of residual tumour cannot be assessed or information is not available

2.1.14 Variable 118. Modality of chemotherapy

Q1: If both neo-adjuvant and adjuvant chemotherapy are administered, do we have to collect only the first (neo-adjuvant) treatment?

R: Yes. Although the collection of both preoperative and postoperative treatment could be more interesting, for the present study we decided to collect only the first treatment.

Q2: Could you please clarify the meaning of "Modality of chemotherapy"?

R: As you can note from the available options, this variable aims to distinguish between the purposes for which it was administered: curative or palliative. The former could be also distinguished in chemotherapy administered in pre-operative (neo-adjuvant) or post-operative (adjuvant) setting – this information is not redundant when the date of starting chemotherapy is lacking – .

2.1.15 Variable 119: Type of chemotherapy (optional)

In several cases a combination of antracycline-taxane or CMF only was administered as type of chemotherapy, but the study protocol does not allow this option.

R: Thanks for this remark. We have now modified the categories/options for this variable as follows:

1 = antracyclines (± CMF)
2 = taxanes (± CMF)
3 = antracyclines+taxanes (± CMF)
4 = CMF only
5 = other drugs and combinations
9 = unknown

2.1.16 Variables 114, 132: Chemotherapy, radiotherapy

In some cases it may happen that women receive one or two sessions of chemotherapy, but it may be later on suspended and replaced by another second-line, or even the dose of radiotherapy is decreased. Where should we record this information?

R: Unfortunately, this is a too detailed information, not always available. Thus we decided not to collect it for the present study and to collect only the first treatment. However, for breast cancer, the information on the conclusion (or not) of the chemotherapy session should be included.

2.1.17 Variable 126: Type of endocrine treatment (optional)

Could you please clarify the meaning of "Type of endocrine treatment"?

R: As you can note from the available options, this variable aims to investigate which class of endocrine drugs was administered – e.g. tamoxifen, aromatase inhibitors, etc -.

2.1.18 Variables 123-125: Date of starting endocrine treatment

For some cases we know that the women received endocrine treatment but the starting date is unknown. However, it is known that this treatment was administered following chemotherapy and/or radiotherapy. What should we consider as date of start of endocrine treatment?

R: Indicatively, we can consider the starting date up to three months after the conclusion of chemotherapy/radiotherapy. However, the protocol allows also the possibility to include only the starting year.

2.2 Colon-rectum

2.2.1 Variable 57: Modality of diagnosis

Q1: It might be confusing to stratify detection mode only in screen-detected and symptomatic tumour. Should opportunistic screening be included in screen-detected cancers? Some cancers are not symptomatic but neither detected in a screening program.

R: The category "screened-detected" indicates either opportunistic or organized screening. Thus, the aim of this variable is to distinguish between symptomatic and asymptomatic cancers. This study design is not appropriate to evaluate the screening programs (case interval, symptoms, screening completeness).
However, the categories/options were harmonised with those indicated for breast cancer.

2.2.2 Variables 76-81: Pre-operative work-up

Could you please clarify "Pre-operative work-up"?

R: This term indicates all the exams the patients underwent before surgery. The most common exams are listed from 76th to 81st variables: echography, thoracic X-ray, thoracic CT, abdominal CT, MRI, echoendoscopy.

2.2.3 Variables 66-67, 70-71, 72-73, 74-75, 111-113: cTNM, pTNM, yTNM and total number of examined and positive nodes

Q1: Is it necessary to collect cTNM if ypTNM is available?

R: Yes, it is necessary and strongly recommended. The clinical TNM stage is very useful in case of neo-adjuvant treatment to understand the stage at diagnosis. In fact, as the main aim of this European HR study is to evaluate the adhesion to internationally agreed clinical guidelines, in the majority of cases the stage at diagnosis is requested.

Q2: If yTNM has to be registered, pTNM should be left blank or other coding is suggested (e.g. not proceed). And if the "neo-adjuvant" treatment was not performed, should yTNM be left blank or else…?

Q3: In case of neo-adjuvant therapy, should we code pT (variable 66) and ypT (variable 111) in the same way? The same question goes to the pair of variables pN (variable 70) and ypN (variable 112). And, how should we code the total number of examined (variable 72) and metastatic (variable 73) nodes?

R: If a neo-adjuvant treatment was performed, ypTNM (ypT, ypN, yM) should be recorded and the pTNM (pT, pN, M) should be left blank. If a neo-adjuvant treatment was not performed, pTNM (pT, pN, M) should be recorded and the ypTNM (ypT, ypN, yM) should be left blank.
As regards the number of examined and positive lymph nodes, if a neo-adjuvant treatment was performed, these numbers should be collected in the dedicated variables (72, 73). For this reason, we modified the "note" in Annexes A/B.

2.2.4 Ex variable 88: Surgical radicality

This variable was dropped because redundant: it did not add anything new to the still available variables on the resection of stage I-III and IV cancers.

2.3 Lung

2.3.1 Ex Variable 60: Tumour biomarker

Could you please make clearer what to consider as: "Tumour biomarkers"?

R: The reply to this question would be: any biomarkers used for diagnosis. However, many tumour biomarkers are currently used, and many of them are a-specific or not prognostic. Thus, it would be better to remove this variable. The only lung cancer biomarker is the EGFR mutation (variable 58).

2.3.2 Variables 70, 74, 76: pTNM

If a patient underwent a tumorectomy with a certain pTNM, and later he/she undergoes a pneumectomy with a new pTNM: which pTNM should we consider?

R: In case of consecutive surgeries, the most extensive/radical surgery (in this example, the pneumectomy) should be recorded as well as the related pTNM.

2.3.3 Variable 84: Surgical radicality

Please clarify meaning meaning and provide a definition.

R: Surgical radicality refers to the complete or incomplete removal of the tumour under study.

As reported in the TNM, 7th version (page 17), the absence or presence of residual tumour after treatment is described by the symbol R. The TNM and pTNM - describing the anatomical extent of cancer in general without considering treatment - can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. The definitions of the R categories are:

RX. Presence of residual tumour cannot be assessed
R0. No residual tumour
R1. Microscopic residual tumour
R2. Macroscopic residual tumour

As you can note, R0 is comparable to our option 1 ("no residual tumour"), RX to our option 9 ("unknown"); whereas, R1 and R2 are both included in our option 2 ("presence of residual tumour").

It is important to underline that for some people the R classification is applicable only to the primary tumour for others it is applicable also to the distant metastases. In such study, we would like to **include** in this definition also the **distant metastases**: in the case of metastatic cancer at diagnosis, you have to select "no residual tumour" only if both the primary tumour and the distant metastasis were completely removed during surgery.

However, we have now modified the definition making it homogeneous with the TNM classification:

1 = R0, no residual tumour
2 = R1, microscopic residual tumour
3 = R2, macroscopic residual tumour
4 = R1/R2, presence of residual tumour but unknown if R1 or R2
9 = RX, presence of residual tumour cannot be assessed or information is not available

2.3.4 Variable 89: Modality of chemotherapy

It is not uncommon the use of Chemo-Radiotherapy concomitant or sequential; we also suggest adding this item.

R: The concomitant or sequential treatments can be derived from the collection of date of starting treatments. We recommend collecting this information not to add new variables.

2.3.5 Variable 97: Modality of radiotherapy

In NCCN 2014 guidelines, apart of pre and postoperative indications, radiotherapy is indicated as a treatment radical in some circumstances:

- Early-Stage NSCLC (Stage I): SABR or SBRT (Stereotactic Ablative Radiotherapy or Setereotactic Body Radiotherapy), or in institutions without an established SABR program, more modesty hypofractionated or dose-intensified conventional fractionated 3D-CRT. It i recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation or in patients with high surgical risk.
- Locally advanced NSCLC (Stage II-III): the standard of care for patients with inoperable stage II and III is concurrent chemo-radiotherapy, or sequential chemo-radiotherapy or RT alone, for frail patients unable to tolerate concurrent therapy.

- Limited stage SCLC (Stage I-III): RT concurrent with chemotherapy is standard treatment, and is preferred to sequential chemo-radiotherapy.

Consider this possibility could be at help for further data analyzing.

R: We agree with this consideration. In the present study, we can evaluate the adhesion to all these NCCN guidelines, except the stereotactic ablative radiotherapy for early stage NSCLC. However, we decided not to collect this detail because not largely available in population-based study.

2.4 Skin melanoma

2.4.1 Variable 57: Modality of diagnosis

Q1: It might be confusing to stratify detection mode only in screened-detected and symptomatic tumour. Should opportunistic screening be included in screened-detected cancers? Some cancers are not symptomatic but neither detected in a screening program.

R: The category "screened-detected" indicates either opportunistic or organized screening. Thus, the aim of this variable is to distinguish between symptomatic and asymptomatic cancers. This study design is not appropriate to evaluate the screening programs (case interval, symptoms, screening completeness).
However, the categories/options were harmonised with those indicated for breast cancer.

Q2: Does the option "symptomatic tumor" include birthmarks (signs)? Most times there are no actual symptoms.

R: Yes. In fact, in these cases, usually, a visit is requested because symptoms or signs are present.

2.4.2 Variable 58: Laterality

Does the laterality refer to the topography of melanoma when occurred in the opposite leg or arm? Should we also consider it if occurred in the head and neck and the trunk and back?

R: The melanoma diagnosed in legs or arms should be considered as bilateral; whereas melanoma diagnosed in the head and neck and the trunk and back are multifocal.

2.4.3 Variable 61: Pattern of neoplastic growth

The pattern of neoplastic growth is no longer in use, therefore it will not be mentioned in the pathological reports.

R: This indication emerged from the common discussion of the HR workshops, thus it is likely that in some countries this information is still in use. When not reported, we suggest to record the option "8= not mentioned in the pathological report".

2.4.4 Variables 73: Breslow thickness

How can we recorded the Breslow thickness equal to 0.6 mm?

R: We have now modified the variable to collect this kind of information.

2.4.5 Variables 73, 87: Breslow thickness, Clark level

In some cases, Breslow and Clark levels are estimated during the excision. But there are cases for which Breslow and Clark levels are also estimated at surgical radicality. Hence, there are other Breslow and Clark levels for these cases. Which is the one we should record: Breslow and Clark levels at excision or at surgical radicality?

R: The Breslow and Clark levels at surgical radicality should be reported.

2.4.6 Variable 87: Clark level

It is indicated that this variable has to be used only for tumours ≤1 mm. What when the tumour size is higher: i.e. tumour >1mm?

R: Since 2002 the Clark level has been used less because it was shown to be less predictive of outcome, less reproducible and more subjective than the Breslow thickness. Thus, it is no longer recommended as a staging criterion. However, there is only one instance in which the Clark level continues to be used to predict prognosis: in patients with thin (≤1.0 mm) melanoma. For this reason the internationally accepted classification system is the TNM staging.

For more details, the following papers may be of interest: Balch CM, Soong SJ, Gershenwald JE, et al. **Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system.** J Clin Oncol. 2001 15;19:3622-34.; Garbe C, Peris K, Hauschild A, et al. **Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2012**. Eur J Cancer 2012;48:2375-90; Dummer R, Haushild A, Guggenheim M, et al. **Melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.** Ann Oncol 2010;21:194-7.

2.4.7 Variable 76: Determination of nodal micrometastases (optional)

The immunohistochemical determination of nodal micrometastases is only done for sentinel nodes.

R: Thank you for this information. However, usually there is a large variability across countries for this procedures, thus we deemed not to specify sentinel lymph nodes in order to leave the possibility to report this information also for other nodes examinations.

2.4.8 Variables 77, 78, 82: Lymphadenectomy, sentinel lymph node biopsy

If both a sentinel node biopsy and later a lymphadenectomy are performed: do we have to sum up nodes from both the biopsy and lymphadenectomy?

R: Yes. However, please remember to also appropriately register the variables related to sentinel nodes (variables 83, 84).

2.4.9 Variable 93: Surgical radicality.

Please, provide the definition.

R: Surgical radicality refers to the complete or incomplete removal of the tumour under study.

As reported in the TNM, 7th version (page 17), the absence or presence of residual tumour after treatment is described by the symbol R. The TNM and pTNM - describing the anatomical extent of cancer in general without considering treatment - can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. The definitions of the R categories are:

RX. Presence of residual tumour cannot be assessed
R0. No residual tumour
R1. Microscopic residual tumour
R2. Macroscopic residual tumour

As you can note, R0 is comparable to our option 1 (“no residual tumour”), RX to our option 9 (“unknown”); whereas, R1 and R2 are both included in our option 2 (“presence of residual tumour”).

It is important to underline that for some people the R classification is applicable only to the primary tumour for others it is applicable also to the distant metastases. In such study, we would like to **include** in this definition also the **distant metastases**: in the case of metastatic cancer at diagnosis, you have to select “no residual tumour” only if both the primary tumour and the distant metastasis were completely removed during surgery.

However, we have now modified the definition making it homogeneous with the TNM classification:

1 = R0, no residual tumour
2 = R1, microscopic residual tumour
3 = R2, macroscopic residual tumour
4 = R1/R2, presence of residual tumour but unknown if R1 or R2
9 = RX, presence of residual tumour cannot be assessed or information is not available

2.5 Lymphoma

2.5.1 Variable 57: Bone marrow exam

What should we consider as acceptable to define the time interval to pick up the bone marrow examination? There are some cases for which more than 1 year has passed between the diagnosis and the completion of this examination.

R: The aim of this variable is to investigate the exams made to confirm the diagnosis of the lymphoma under study. Thus, indicatively it should not be performed within 1 year since diagnosis.

2.5.2 Variables 67, 70: LDH and β2 test category

There option "lower than the lower normal limit" is lacking. Should we code it as 1=normal?

R: Yes, we agree with recording the lower values than the normal limit as "normal". Please note that during the HR workshop wee held in Milan in 2013, it was decided to drop this option/category as well as the lower than normal limit (not meaningful).

2.5.3 Variables 69, 72: Higher LDH, higher β2

Could you please clarify: "LDH value" and "Higher LDH". The meaning of "To be collected ONLY if the LDH test category was not available" is unclear. The same applies to the β2 microglobulin.

R: During the HR meeting held in Milan last year, it was decided that the most important variable related to LDH is the LDH category. However, if this information is not available but the LDH value is available, then the information on the upper limit is necessary. The same explanation can be applied to the β2 microglobulin.

2.5.4 Variables 74-75: Reported and reconstructed Ann Arbor stage

Why is Ann Arbor staging stratified in reported/reconstructed? Is there any implication for the patient?

R: No, there isn't. During the HR Workshop held in Milan in 2013, it was decided to distinguish between the two different staging modalities as this is important during the quality check or in presence of not completely clear situations.

2.5.5 Variables 83-94: Extranodal localisations at diagnosis

Q1: What is the time interval or cut point we should consider: before 3 months or after 3 months?

R: We have now added in Annexes A/B the note on the cut-point: *"(within 3 months –after or before– from diagnosis)"*

Q2: If the lymphoma is primary located in a specified organ (e.g., nervous system) instead of the nodes, should we code 1=present on the location of the tumour among the variables 83-94?

R: Yes, you should record "1=present" in the specified organ.

2.5.6 Variables 122-125: Transformation from FL to DLBCL.

Could you please clarify? We were wondering where to collect information on other transformations.

R: The aim of this item is to collect the possible transformation from Follicular lymphoma (FL) to Diffuse Large B-cell lymphoma (DLBCL). Thus, it could be collected reviewing the clinical records for both FL and DLBCL if there is a sufficient time interval between the diagnosis and the cancer registration. Alternatively, for FL it could be collected in the future in case of a follow-up update.

3. Notes on the Access databases

All the recorded cases are saved in the table named 'tlbBancaDati'. Additionally, all variables were ordered in the "tlbBancadati" according to the numbering in Annexes A/B and each variable was labelled with the corresponding number. In this way, the linkage between the external sources and the Access database is simplified.

Each database (DB) request only once the input of the name of your Cancer Registry and to save a recorded case, a minimum number of variables is requested:

- patient identification code
- gender
- date of incidence.

The size of databases depends on the number of tables built for the definition of the different variables needed for the data collection. Thus, it is possible that the size of databases is different from each other. If you have some problems related to the rapidity of imputation, we suggest opening only one database at a time.

If not explicity requested, each DB is in Access 2007 version.
Please, pay attention when you open a database Access 2007, because you could see the **Message Bar** "Security warning Certain content in the database has been disabled". In such a case, please follow the following instructions:

- click **Options** on the **Message bar**: you will see a dialog box that has the **Disable content** check box selected
- select the **Enable this content** check box, and then click **OK**.

The result of these steps is that all the executable content in your database now functions as it was designed by the developer.

Q1: Entering information in the database would be faster if you could change from one variable to the next one orderly using the tab key. It would be also useful to avoid missing or incomplete variables.
Q2: After complete data for one record (patient) I can not continue for next patient. I have to exit and next start apllication again.
Q3: The date fields do not accept combinations of 99 or 9999 as instructed.
R: A new version of each database is now available, including all suggestions we received.
In particular, as regards dates, it was included the possibility to record combinations of 99 and 9999. However, due to this change, after filling in the dates the "/" are no more evident but they are present in the final and saved database.
Additionally, the button "new patient" was included, to insert a new case without exiting and starting the application again. However, it is possible that in some registries this button doesn't work. In this case, please contact your IT personnel, because the problem could be related to your internal hardware/software settings.

Q4: We have to scroll down to see the end of the screen of application: there is empty space below data entry so please make this view on one screen – it may be more convenient.
R: Unfortunately, the "white" space is evident only in the sheets where few variables are collected, but is not so evident for example in those related to treatments and co-morbidities.
Take note, however, that the white space depends on the size of your screen.

Q5: The database crashes if we try to insert data into fields Cause of death and ICD10 for second cancer (no matter whether entering a valid ICD code or 999.9). It stops working and does not allow saving or moving on to other fields.
R: At the beginning, an internal control was included. However, due to the different hardware/software settings, it is possible that these two variables did not work. We hope to have now solved the problem.

4. List of changes

It refers to the Annexes A/B circulated on August, 10 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma
1. Variables with changes in options/categories:					
1.1 LDH value and higher LDH					X
1.2 β2 microglobulin value and higher β2 microglobulin					X

5. Old updates

5.1 Version 2.2

It refers to the Annexes A/B circulated on May, 22 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma
1. Variables with changes in options/categories:					
1.1 Microscopic involvement				X	

5.2 Version 2.1

It refers to the Annexes A/B circulated on May, 7 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma
1. Variables with changes in options/categories:					
1.1 Breslow thickness				X	

5.3 Version 2.0

It refers to the Annexes A/B circulated on March, 20 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma
1. Extension of data collection					
1.1Treatments to be collected also for M1 cancers	X				
2. New variables *(included as optional)*					
2.1 Site of distant metastasis	X		X	X	
2.2 Cut-off for Oestrogen, Progesterone, Ki67 and HER2 positivity	X				
3. New variables *(included as mandatory)*					
3.1 yM	X				
4. Variables with changes in options/categories:					
4.1 Surgical radicality	X		X	X	
4.2 HER2 and FISH	X				
4.3 Oestrogen, Progesterone, Ki67 and HER2 percentages/ranges	X				
4.4 Grading	X	X	X	X	X
4.5 Type of chemotherapy	X				
4.6 Modality of diagnosis		X		X	
5. Dropped variables					
5.1 Redundant variable on surgical radicality		X			
5.2 Tumour biomarkers			X		

5.4 Version 1.2

It refers to the Annexes A/B circulated on January, 27 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma

1. New variables *(included as optional)*	
1.1 yTNM stage	X

5.5 Version 1.1

It refers to the Annexes A/B circulated on January, 15 2014

Changes	Breast cancer	Colorectal cancer	Lung cancer	Skin melanoma	Lymphoma
1. New variables *(included as mandatory)*					
1.1 cM	X	X	X	X	
1.2 Date of incidence of second (subsequent) cancer	X	X	X	X	X
2. Variables with changes in options/categories:					
2.1 Inclusion of ">900 mm" category in the tumour size (both clinical and pathological)	X	X	X		X
2.2 A category related to response to treatment					X