15th Dec 1999

UPDATED PROTOCOL OF THE EUROCARE HIGH RESOLUTION STUDIES ON CARE OF CANCER PATIENTS

INTRODUCTION

Eurocare is a "Concerted Action" of European population-based cancer registries (CRs) which deals with survival and care of cancer patients.
On the basis of the past experience of Eurocare, the collection of some clinical variables (stage and basic diagnostic investigations performed for staging, therapy) has been included in the **Eurocare-3 Survival Study** for most solid tumours. This will help in interpreting intercountry and overtime survival trends, performing proper stage specific comparisons.

The collection of more detailed clinical information will continue through the **high resolution studies** for the following tumours:

- Breast, colorectal and testicular cancer, for which the Eurocare forms have been updated as described in the present protocol
- Prostate cancer, for which a new form has been developed

The previous high resolution studies, carried out on samples of patients diagnosed in 1990-91 demonstrated that at least some CRs are able to collect detailed clinical information on stage, staging procedures, diagnostic exams and therapy. The type of clinical information which is requested is basically the same as in the previous high resolution studies, and the forms were modified only slightly, in order to integrate them into the existing high resolution databases. The main innovation proposed by the present protocol regards the collection of information on the clinical follow-up of patients. The occurrence of a relapse, distant metastases and another primary tumour is now considered.

1. RATIONALE OF THE STUDY

In most Cancer Registries information on stage and on diagnostic and therapeutic procedure is incomplete and/or not standardized. This makes the interpretation of cancer incidence and survival trends difficult.

Survival comparisons of cases at the same stage cannot fully explain survival differences, due to stage migration. Stage is in fact highly sensitive to the diagnostic procedures used to define it, and new procedures are constantly being developed, particularly those able to reveal occult metastases. As a consequence, cases recently staged as 'localised' are more likely to be localised than in the past, with consequent better prognosis, while cases with previously unrecognised metastatic spread are now more often recognised as metastatic. In addition more recent 'advanced cases' will perform better than in the past, because of the inclusion of less advanced metastatic cases, that previously were classified as localised. The same considerations apply to intercountry comparisons.

Proper stage specific comparisons therefore should take into account the diagnostic exams performed for staging.

Most studies on care are carried out in clinical settings, comprising one or more hospitals, and clinicians, who directly take care of patients, are usually involved. These studies may simply describe how patients are assisted, or may also evaluate the care procedures which are adopted in one or more hospitals in relation to a "golden standard" or to the average level of the institutions participating in the study. A limitation of these hospital-based studies is that they may not be representative of all the health facilities existing in a defined area.

Population-based cancer registries, on the contrary, may check the diffusion of some selected care procedures in current clinical practice, independently from any factors that could affect the access of patients to certain hospitals.

The project on care will include COLORECTAL, FEMALE BREAST, PROSTATE and TESTICULAR cancers.
The reasons for choosing only these cancers can be summarized as follows:

1) Colorectal, female breast and prostate cancers are common tumours, with high public health priority
2) They are likely to be treated in general hospitals, and not only in specialized structures, so that the variability in care can be high and detectable by relatively few items.
3) Guidelines for diagnosis and treatment are available
4) For prostate cancer, the diffusion of recent means of diagnosis will make the interpretation of survival (and incidence) time trends difficult. The increasing use of PSA, transrectal ultrasonograpy and transuretral resections of adenomas will increase the diagnosis of cancers in preclinical phase, whose natural history is different than that of cancers detected because of clinical signs. Also, the treatment of low stage and asymptomatic prostate cancers is not well established.
5) For testicular cancer, the extent of intercountry differences in survival is smaller than that found for other cancers. The high curability of this tumour allows 100% patients cured as a theoretical golden standard to be reached by all countries. A survival as close as possible to these figures can be considered an indicator of effectiveness of health systems. Thus, a main aim of the high resolution study is to study the clinical characteristics of cases with unsuccessful outcomes. The study will be continued according to the existing protocol (see attached).

2. AIMS OF THE STUDY

- To describe and to compare care in representative samples of cancer patients in Europe.
- To make proper intercountry and overtime survival comparisons, taking into account stage and diagnostic exams performed for staging.
- To set a basis for future surveys, in order to describe time trends of patterns of care for cancer.
- To explore the feasibility of describing clinical events following diagnosis, specifically: local recurrences, distant metastases and the occurrence of a further primary tumour. This will enable us to study the time of progression of the disease and to describe survival after relapse.

- As a side result, this information can be used also for computing prevalence dividing the patients into those living in a disease-free status and those requiring care for a relapse of their cancer.
- To update follow-up of the patients already included in the previous high resolution studies on breast, colorectal and testicular cancer. These are patients diagnosed between 1990 and 1991.

3. STUDY DESIGN

BREAST, COLORECTAL and PROSTATE cancers

The minimum study dimension is 500 cases per registry for each tumour. Cases will be sampled among those incident from **1996 to 1998, preferably 1997**, extended either backward or forward, in order to reach the requested number of cases. For registries of great dimensions, the best approach for a sampling procedure would be choosing a time interval between 1996 and 1998 for which expected incident cases are at least 500.
All the cases diagnosed in the chosen period must be included. The recruitment will therefore be considered complete when all current procedures for data collection and quality control have been completed.

As for the previous high resolution studies, all the relevant clinical notes (both as in- and out-patient) of a patient are to be reviewed, in order to reconstruct the clinical history. Each registry will individuate the most appropriate source of information to describe follow-up.

This revision is expensive and requires trained personnel. For this reason, a financial support for this labour is envisaged by Eurocare-3. However, given the limitations of the budget, only a few registries can be funded.
Therefore the registries are encouraged to apply for funds in their countries or in international study projects calls (e.g. E.C. projects).

4. CRITERIA OF INCLUSION

For the high resolution studies, all the incident cases of colon and rectum (ICD-9 153-154), female breast (ICD-9 174) and prostate (ICD-9 185) cancers occurring in the relevant period are to be included.

Only malignant invasive and in situ tumours will be considered, as defined by the ICD-0 morphology code ending with 3 or more. Uncertain and borderline tumours will be excluded. Both histologically verified and not verified cases will be included.

Cases notified by their death certificate only (DCO) and cases discovered at autopsy will be notified through a specific form.

A tumour of breast, colorectum, prostate or testis diagnosed after another primary cancer is to be included only if the first tumour occurred in a different organ. Second contralateral breast cancer and second colorectal cancers therefore will not be notified as independent cases.

Synchronous bilateral breast cancers and multiple synchronous colorectal cancers will be included and treated as a single case; both localizations will be recorded, as well as the most advanced stage.

The occurrence of a second primary tumour following the first which is included in the present study, will be recorded in the block of follow-up, as well as recurrences and metastasis.

5. DATA TO BE COLLECTED FOR COLORECTAL (ICD-9 153-154), BREAST (ICD-9 174) AND PROSTATE (ICD-9 185) CANCER IN THE "HIGH RESOLUTION" STUDY.

INSTRUCTIONS FOR FILLING- IN THE FORMS

5.1 IDENTIFICATION CODE.
This 10 digit variable is necessary for editing and quality controls purposes. It should enable us to retrieve a specific record in the registries to check for errors and incongruences, and for follow-up purposes. It is recommended to use the same identification code of the cancer registry files. A numeric or an alphanumeric variable can be used.

5.2 PREVIOUS MALIGNANT TUMOUR
If a previous (or another synchronous) malignant tumour was diagnosed, its site will be recorded. ICD-9 code will be reported optionally.

5.3 SEX. FOR COLORECTAL CANCERS

5.4 YEAR OF BIRTH.
Year of birth must be registered using a four digit variable,
e.g. |1|9|4|5| or |1|8|9|9|.

5.5 DATE OF DIAGNOSIS AND DATE OF FIRST HOSPITAL ADMISSION (OR ATTENDANCE AS OUTPATIENT).
These two dates are requested in order to help standardizing the definition of date of diagnosis.
The date of diagnosis usually recorded in the cancer registry will be reported. The date of the first hospital admission or of the first visit during which the tumour was diagnosed will be reported as well.

5.6 MARITAL STATUS.
Mark the relevant box

5.7 OCCUPATION OR SOCIAL CLASS INDICATORS OPTIONAL
A standardized socio-economic indicator for cancer registries does not exist. Moreover, the availability and the completeness of this information varies from registry to registry. Every centre will record the available data, if any, on the last

relevant occupation of the patient (of the breadwinner if the patient is a housewife, unemployed or retired).
The socio-economic indicator chosen will be written in detail, as stated in the clinical notes.
This variable will be coded by the coordinating centre.

5.8 PRIMARY TUMOUR SITE.
Site will be written in detail. ICD-9 code will be reported optionally.
The presence of bilateral synchronous (breast) or multifocal (colon-rectum) cancers will be recorded. The ICD-9 code will refer to the most advanced cancer.

5.9 MORPHOLOGY.
Morphology must be written out. The type of histological confirmation has been added for colorectal and prostate cancer.
Histological grading is of particular prognostic importance for prostatic cancer: pick the relevant box and circle the Gleason score as recorded in the clinical or pathology reports.

5.10 INCLUSION OF THE PATIENT IN A CLINICAL TRIAL.
If explicitly mentioned in the clinical notes, the information will be indicated in the form.

5.11 STAGE
The pathological stage is to be reported, if available. When it is not available the clinical stage is to be reported.
Stage is to be indicated as recorded in the clinical notes and as reconstructed by the registrar, (for breast and colorectal cancer) according to TNM classification (TNM Atlas, third edition, 2nd revision 1992).
For BREAST cancers, the size of the tumour in millimetres will be recorded, when available. Size is that measured by the pathologist or, in absence, by radiologist/clinician.
For COLORECTAL cancers both pTNM and DUKES classification are envisaged.
For PROSTATE cancer, a simplified pT classification is also envisaged, to be used if the detailed T is not available: localised (pT1-pT2) /advanced (pT3-pT4)

5.12 For all tumours, THE NUMBER OF LYMPH-NODES WITH METASTASIS AND THE TOTAL NUMBER OF LYMPH-NODES EXAMINED by the pathologist is to be reported.

5.13 DIAGNOSTIC PROCEDURES PERFORMED.
Basic diagnostic examinations regarding COLORECTAL, BREAST and PROSTATE cancer are listed in the form.
This information should make it possible to distinguish whether the examination has been performed and, for breast and colorectal cancers, to know the reasons for not having performed it,

5.14 SURGERY.

The detailed type of surgery is to be recorded.
COLORECTAL cancers: three lists of surgical procedures are listed, one for colon cancers, one for rectal cancers and one for both these localizations.
BREAST cancer: common surgical procedures are listed
PROSTATE cancer: surgery is distinguished in prostatectomy (any type) and transuretral resection (TUR).

5.15 AXILLARY LYMPHADENECTOMY For BREAST CANCER

If it was performed it is to be recorded, specifying if the purpose was for clearing or for sampling nodes.
In the present version of form, the sentinel lymph-node biopsy has been added, since this technique is becoming increasingly used. If a clearing axillary lymphadenectomy is performed following the results of the lymph-node examination, it is to be coded in the relevant box.

5.16 HORMONAL RECEPTORS. For BREAST CANCER

Their determination will be recorded, and, when available, the results will be specified.

5.17 CASTRATION. For BREAST CANCER

It is requested to specify whether it was performed by surgery or by radiotherapy.
Chemical castration with GnRH analogues is to be coded under endocrine treatment.

5.18 COLOSTOMY OR ILEOSTOMY For COLORECTAL CANCER

The existence of a colostomy or ileostomy is important to study the period of survival that is affected by handicap due to therapy. Temporary and permanent colostomy are to be distinguished.

5.19 PATHOLOGICAL OR SURGICAL For COLORECTAL CANCER
EVIDENCE OF RESIDUAL PRIMARY TUMOUR.

This information will be collected from the description of surgery and/or from the pathology report. The information is collected to establish whether surgery was deemed to be radical or not.

5.20 DATE OF SURGERY

Dates of therapies are necessary to determine the sequence of the therapeutic procedures which have been performed. Day, month and year of surgery will be collected.
For COLORECTAL cancers, it is intended to investigate whether surgery was planned or the patient was operated in emergency.

5.21 REASONS FOR NOT PERFORMING SURGERY/ CHEMOTHERAPY/ ENDOCRINE TREATMENT/ RADIOTHERAPY.

This item is an indirect indicator of comorbidity that can limit therapy.

Some possible reasons for not performing surgery (or chemotherapy/endocrine treatment/radiotherapy) are reported in the form. This information should make it possible to determine whether serious comorbidity was mentioned in the clinical record.

If a given therapy was not indicated by treatment protocols, the reasons for not performing it will be 'other or unspecified'.

5.22 CHEMOTHERAPY/ENDOCRINE TREATMENT/ RADIOTHERAPY/OTHER MEDICAL THERAPIES.

First therapy against the relevant cancer is to be recorded, usually treatments performed within 6 months from diagnosis. Treatments for relapses and for subsequent mestatasis are not to be considered in these blocks.

The type of therapy (e.g. chemotherapy regimen, dose of radiation) will not be considered in the study.

Cases for which one therapy, e.g. chemotherapy has been started but interrupted for any reason will be considered as "Chemotherapy Yes", considering the 'intention to treat', rather than the completeness of the therapeutic cycle.

PROSTATE cancer:

Hormonal therapy includes female sex hormones, LHRH analogues, anti-androgens (steroidal and non-steroidal)

BREAST cancer:

Hormonal therapy includes sex hormons, tamoxifen, other SERM GnRH analogues, aromatase inhibitors and other.

5.23 DATE OF BEGINNING OF CHEMOTHERAPY/ENDOCRINE TREATMENT /RADIOTHERAPY.

Day, month and year of beginning will be recorded in order to determine the sequence of therapies and check that therapy has been actually performed for the relevant primary tumour.

5.24 STATUS OF THE PATIENT **at the end of 31st December 2001.**

In case of death, the cause of death and ICD code of the disease causing death is to be reported.

5.25 FOLLOW-UP. A block on the clinical follow-up has been added in the revised forms for the high resolution studies. This part is to be filled in through the consultation of the clinical notes, referring to treatments and exams performed as in- or out-patient. The source of information for this part of the study can vary from country to country and also by areas within a country. Each registry should individuate the best source of information.

Only a few events following diagnosis will be considered, with the dates of occurrence:

Local/regional recurrences: includes recurrences of the disease in the anatomic regions adjacent the tumour. E.g.: a recurrence in the same breast where surgery was performed, or in the regional lymp-nodes. Please write in detail the site of recurrences.

Distant metastasis, as usually defined by TNM. Please write in detail the site of metastasis.

Primary tumour/s following that in study. The date of diagnosis and the ICD-9 code is to be reported. The diagnosis of a second contralateral breast cancer or of a second colorectal tumour is to be reported in this box.

The date of the last clinical information refers to that of the last check made by the registry, regardless of the occurrence of one of the above mentioned events. Only the last date will be considered in the analysis.

By **31st December 2001**, all the included cases should have been followed for at least 3 years. All the clinical events (recurrences, metastasis, other primary tumour) occurred during this period are to be reported in the relevant block. Subsequent checks will be organised centrally, as for the other Eurocare studies.

5.26 Before submitting the form, please check that all blocks have been duly filled in.

6. SUBMISSION OF DATA.

Data checks and basic analyses will be performed at the Division of Epidemiology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy (co-ordinating centre).

For all tumours, the required information will be reported on specific forms that have been prepared and distributed by the co-ordinating centre. When data collection is concluded, the forms will be returned to the co-ordinating centre, in which data input and editing will be performed.

Alternatively, a computerised programme for the direct data input to be performed by the registries will be made available.

In order to ensure the completeness of sampling, i.e. that all the cases occurred in the chosen period, for each registry data collection will be considered concluded when the relevant incidence period is completed.

Data are to be submitted to the data analysis centre in Milano **by 30th June 2002**