November 30,2012

MINUTES OF THE
EUROPEAN HIGH RESOLUTION STUDY WORKSHOP
HELD ON 06.11.2012
AT THE MALPENSA CENTER OF MILAN
MALPENSA AIRPORT, ITALY

The Meeting was opened by Dr Milena Sant, PL of WP9 "Cancer Data & Information" in the EC funded- EPAAC Joint Action, who introduced the background for the need and opportunities linked with the realization of new High Resolution Studies (HR) involving as many Member States of the European Union as possible, and illustrated the aims of the day.

BACKGROUND

- High Resolution studies are carried out using population Cancer Registry (CR) data on a sample basis, involving the collection (and study) of detailed information on diagnostic, therapeutic and follow up procedures that are not usually routinely collected by CRs.
- Past HR studies compared patterns of care across Europe and investigated reasons for survival differences highlighted by EUROCARE (EUROpean CAncer REgistry-based study on survival and CARE of cancer patients).
- HR studies were carried out on testicular and stomach cancer (diagnosis 1987-93), breast and colorectal (diagnosis 1990-92), breast, colorectal and prostate cancer (1996-98), and lympho-prolipherative neoplasms (HAEMACARE), with the involvement of a large number of European cancer registries in many countries.
- HR studies on breast, colorectal and prostate cancer were also started in the framework of the CONCORD project, comparing patterns of care and survival across continents.
- The GRELL group (Groupe des Registres et d'Épidémiologistes de Langue Latine) started developed HR data analyses in Italy, Spain and France on colorectal and breast cancer.
- The EU Joint Action EPAAC (2010-2013) has as goal of its WP9 the definition of a European Cancer Information System (ECIS). The present workshop is promoted as part of WP9's discussion on the standardised cancer control indicators that are to be made available in a future ECIS, including patterns of care.

AIMS OF THE DAY

- To identify possible researchers who would be interested in participating in one or several collaborative HR studies and discuss any obstacles to the development of such studies;
- To identify the most suitable cancer sites, and most appropriate period, for the study;
- To discuss practical organisational issues linked with HR studies (e.g. Data collection method, sampling);
- To discuss funding possibilities.

SESSION 1 - CONTRIBUTES (CHAIR DR FRANCO BERRINO)

1. Information on the existing HR experiences involving Cancer Registries (CRs) in the EU were provided, i.e. from Italy, France, Spain, the Netherlands, the UK, Denmark, Germany, Poland, Switzerland, Belgium and Portugal. The following table offers an overview.

	HR STUDIES	STUDY PERIOD	TYPE	OUTCOME	FUNDING SCOPE
Italy	breast, colorectum, NHL,melanoma, lung, prostate*	2003-2005 *(1996-1999 and 2005-2007)	sample, retrospective data collection, , *proportion cured and mean survival time of fatal cases	survival, pattern of care	dedicated funds, research grant
France	breast, colorectum, NHL,melanoma, prostate, lung	selected years	prospective, entire incidence in the year	patterns of care	Moh, research
Spain	breast, planned colorectum	2004-2005	All incident cases, retrospective data collection	patterns of care, moleculars patterns &survival, comorbidity &survival	dedicated MoH funds , research
NL	several tumour sites	several years,	samples, either retrospective or prospective	survival, patterns of care, specific aspects, e.g. comorbidity	research, audit
UK, ICBP**	breast, colorectum, ovary, lung	2000-2007	retrospective	survival, patterns of care	dedicated funds, research
DK	national clinical registries for many cancer sites, link CR	since the 90's, but depending on site	prospective	patterns of care, but survival also possible	audit
Germany	several sites, planned within a wide National study, involving all CRs (DKFZ)	(1997-2006)	prospective data collection with National coverage starting within the next few years	survival	MoH funds for public health audit, research
	BC survival (Saarland)	(1993-2008)	Samples, retrospective data collection	survival	research
PL	EU3 HR studies	1997-98 and 96-98			MoH funds
	breast	2000-2002	retrospective	patterns of care; urban–rural survival	Research grants (Min. Science)
Switzerland	prostate(planned) end of life for several cancers (ongoing)			patterns of care	
Belgium	breast, prostate			patterns of care	MoH funds public health audit
Portugal	Melanoma, planned breast colorectum				

**The ICBP Module 5, initially designed as a high-resolution study on sample basis, is now focused on collecting details of "routine" electronic data feeds to evaluate the feasibility of a pattern of care study reporting more up-to-date comparisons of current practice

2. An insight on rare cancers was presented by Annalisa Trama. High resolution studies are envisioned in a dedicated Italian project on rare cancers on neuroendocrine tumors and pleural malignant mesothelioma. High resolution studies are envisioned also at European level in the context of the project « Information network on rare cancers » (RARECARENet). The latter will focus on neuroendocrine tumours, testicular cancer, soft tissue sarcomas, and head and neck tumours. The Italian project was supported by the Italian MoH while RARECARENet was supported by the Executive Agency for Health and Consumers of the DG Sanco. The HR studies are envisioned to start in 2013.

3. A proposal for a new collaborative European HR study was presented by Milena Sant, covering the main aims and a preliminary selection of variables to be discussed.

Proposed aims:

- To study survival differences
- To analyse different policies of using of new treatments
- To improve quality of CR data, expanding content for outcome and quality of care studies
- To study co-morbidity, and metabolic factors such as body mass index (BMI) and glycaemia, for selected cancers

Two approaches: "prospective" or "retrospective" study

- A retrospective study is based on past incidence cases for whom a sufficiently long follow up time is available. For instance in 2013, with patient life status updated to 2011, a 5-yr follow up length is available for patients who were diagnosed in 2006. This approach is useful to study both patterns of care, as well as their impact on survival;

- A prospective study is based on cases diagnosed more recently, typically those cases diagnosed in the latest or current year of registration. As cases are registered to be included in incidence series, additional information on care items can be added at the same time to the variables usually recorded by the registry. This approach is useful to obtain timely information on patterns of care and allows for descriptive analyses on the frequency of procedures or adhesion to guidelines. A limit of this approach, however, is that outcomes (i.e. impact of care procedures on overall or disease-free survival) can only be evaluated at a later stage, when an adequate follow-up length will be elapsed. Moreover, sampling procedures should be evaluated: for instance, in order to draw unbiased samples with respect to the whole incidence series, it would be appropriate to include in the study a period of complete incidence, e.g. one year of complete incidence.

The first approach is that adopted in the conventional EUROCARE high resolution studies for outcome studies, whereas the second approach is that adopted in health care "process" studies.

SESSION1- DISCUSSION & DECISIONS

The importance of studies on recent data and information flows and /or integration with clinical databases was raised during discussion.

Some CRs (Sweden, Denmark and the Netherlands) now collect TNM 'on a regular basis' due to the availability of these data or to work with clinical databases to complement the routine collection performed by CRs (Denmark, Germany, Belgium).

Clinicians should be involved early in the process, to collaborate in designing innovative and relevant study protocols.

The following issued were raised: problems of comparability with regard to staging criteria and type of treatment encodings (Nordic countries). Problems with access to clinical data and linking with clinical registries (lack of systematic collaboration agreements, collaborations only voluntary limits on access-related legislation).

HR studies are mainly aimed to explain the reasons of the survival differences highlighted by the EUROCARE main analyses, through the collection of more detailed information than that collected in the routine activity of CRs. HR studies focus on public health and are useful to evaluate the dissemination of new treatments, and their effectiveness (= efficacy in the whole clinical practice). By contrast, studies based on hospital sets of patients and controlled clinical studies are aimed to investigate the efficacy of treatments or diagnostic procedures, using sets of patients with selected characteristics (e.g. age, stage, bio-molecular characteristics).

Among the limits of classical HR studies, problems of representativeness of cases were raised, with resulting difficulties with respect to harmonizing conclusions, publication and funding.

Most participants expressed their support towards the prospective approach, even if the evaluation of outcome would be limited or postponed compared to a classical HR study. It was noted, however, that the two approaches differently suit different cancer sites or different study objectives. The choice of approach for recruiting cases, as well as the period of diagnosis should not be made in advance or in general, as it may depend on the objective of the study, (e.g. 2 years of follow-up can be sufficient for some cancer sites and for certain outcomes).

As a contribution to the common discussion, EPAAC WP7 leader Jose Borras remarked that in the next 2-3 years clinical guidelines will be available for at least selected cancers, it should therefore useful to promote population based studies investigating and comparing adhesion to guidelines. Also the comparison of existing guidelines across countries would be an interesting topic of research. In this view, the prospective collection of data would be more effective and sustainable than the traditional HR studies based on retrospective sampling and data collection.

The discussion allowed to find a shared vision on the aims and the opportunity of a possible EU HR study, and a common interest to proceed with HR prospective studies emerged in the day.

The sites that were proposed for investigation, under criteria of high scientific significance and past experiences, are: breast, colo-rectum, prostate, lung, stomach, skin melanoma, testis (rare cancer), haematological malignancies.

A list of cancers suitable for a common European study will be proposed. A protocol will be drafted and discussed in early 2013, and other EU CRS will be invited to consider participation. As a first step, existing HR protocols will be analysed as from December 2012.

ACTIONS: Thank you for sharing protocols and published papers on HR studies

SESSION 2 – **CONTRIBUTES** (CHAIRED BY JEAN FAIVRE)

1. The Italian HR protocol on lung cancer and some preliminary analyses of Italian HR data was presented by Pamela Minicozzi, with the aim of highlighting and discussing the issues of representativeness of the HR samples to the entire patients' population in the areas, and statistical power. The rationale for the number of cases included in the Italian HR study was illustrated.

Discussion
In order to increase representativeness of cancer cases diagnosed in a single country, a stratified sampling is more appropriate than the simple random and systematic samplings. For prospective data collection, sampling criteria should be discussed.

2. HR data from archive tissue analysis were presented by Giorgio Stanta, from the Organization of European Cancer Institutes (OECI) "Biobanks & Molecular Pathobiology Group", who illustrated the tremendous potential of tissue archives that are currently available in all hospitals, allowing the bio-molecular characterisation of most cancers. This possibility greatly helps research and may help properly investigate the appropriateness of introducing new treatments. However, problems of method standardisation should be carefully considered. In addition, the characterisation of small cancer subgroups may involve problems in establishing the number of cases necessary to obtain significant results.

Discussion
HR analysis from archive tissue are potentially very powerful, however results are often not harmonised between laboratories. It is very important to understand which biomarkers have to be included in a HR study for each cancer.

3. The EPAAC proposal for a European Cancer Information System was presented by R. Capocaccia. The possible types of study design for the collection of high resolution variables and their different roles within a European cancer Information System were outlined. In particular, the characteristics of the retrospective, ad hoc HR studies, funded on a project base, were compared to those of the prospective and systematic studies, to be carried out under a sustained funding. The different objectives attainable by these two types of study were briefly discussed.

Discussion
The discussion pointed out that the type of information to be collected, and in particular its level of detail, does not depend on the time perspective of the study (retrospective vs. prospective), but more on its continuity. Ad hoc studies, aimed to answer specific questions, can be designed to collect still not fully standardized and not previously tested information items with respect to systematic studies, planned to be carried out with time continuity and on a sustained basis

4. The possible sources of funds for a EU HR study was presented by Paolo Baili. Two possibilities exist: EU funding bodies calling for specific projects vs the creation of a scientific consortium constituted by all researchers contributing with data (ie based on single CRs or national funding). The first option will depend on new calls to be issued by the EU not before Spring 2013.

Discussion

At the moment no resources are immediately available for funding HR studies.

One possibility could be to ask each country to fund itself at national level, in view of applying for a call.

Scientific societies and pharmaceutical industries were suggested as possible funding sources.

Some registries are committed and funded by the government or other national bodies for collecting data on patterns of care prospectively, thus the data collected in this frame could be included in a European HR study. Uniform study protocols are necessary in order to have comparable data and interpretable results.

GENERAL DISCUSSION AND CONCLUSIONS

- There is a shared interest to work for the development of a EU HR study as a group.
- A protocol will be drafted to accommodate the adoption of both approaches for both "retrospective" and "prospective" data collection, where possible, and taking in consideration the limits raised during discussion.
- All existing initiatives will be considered as a necessary prerequisite to designing innovative and relevant study protocols
- Early in the process (since the protocol drafting) clinicians must be involved.
- The next meeting of the EU HR study group will be in ISPRA at JRC to discuss a protocol, early 2013 (TBD).
- On funding: let's explore the possibility of a EU project but in the meantime let's focus on local initiatives and scientific societies able to provide funds.
- EPAAC WP9 but also WP7 and WP8, will be involved in the promotion of this HR activity
- **For those who have not yet done so, please send your HR protocols, as soon as possible.**

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