State of the art of use of clinical databases and treatment registries in evaluating cancer care

Deliverable 6.5
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JWW Coebergh: workpackage leader
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Summary WP6: Cancer Registries and clinical databases

WP6 – Interface between cancer registries & clinical databases: population-based clinical evaluation
Jan Willem Coebergh1,2, Corina van den Hurk1,2, Valery Lemmens3

Background

Aims: enable & perform population-based studies of process & outcome of cancer care
- Define place of CRs within oncological care: population-based
- Recommend essential data items for quality assurance & monitoring of cancer services
  - Stage & staging (clinical & postoperative)
    - Aggressiveness: grade, MAI
  - Primary treatments & (date)
  - Optional: Recurrence & progression (project basis) & treatments
  - Optional: Complications & specific side effects
- Probabilities for analyzing clinical data & registry-derived indicators in evaluating cancer care with respect to guidelines
- Examples of unique position of the CR in the domain of clinical oncology:
  - Genomic oncology
  - Referral patterns to & utilization of radiotherapy
    o In primary treatment
    o In treatment of recurrence & progression
    o Multiple primaries as potential side effect
  - Link CR data with clinical databases:
    o Study adherence to country-specific guidelines of cancer treatment
    o Text-book knowledge

Linkage Clinical Databases

- Aims of linkage: No double work & strengthen each other: synergy
- Clinical databases only additional to CR′s if sufficiently clinically oriented
- Trust needed of clinicians in CR data (fu w)
  - Involved in choices for data collection
  - Regional & local feed back essential for adequate interpretation
  - Following changes implies curiosity & interest
  - Start using already existing data & use results from best practices elsewhere
    o Radiotherapy databases
    o Pharmaco-epidemiological registries on drug utilisation
- CR′s helpful for:
  - Registration: less waste of time in hospital,
  - Increase validity
  - Training of – independent – registrars
  - Data validation of /with clinical database
  - Follow-up: link with care process
  - Timeliness of CR′s needed: for assessment of quality of care
  - Not possible in many European CR′s: limited data access &/or resources

CR in general

- All data that are collected should be used
- Extra collection of items must be accountable
  - Always start small & grow in the process
  - Use of data: open access to anonymised data?
    - Specialisation needed
    - Use publications of other CRs (as a start)
- Examples of usage of CR data for clinical evaluation:
  o Cancer in the elderly
  o Quality of life studies
  o Phase IV studies of targeted drugs
  o High/low resolution studies: European variation
    - Only with ‘willing’ regions/countries
  o Hospital variation
    - Only with feedback
  - Regionalisation of complex care
    - Referral as important as concentration

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1 INTRODUCTION

With respect to population-based oncological care evaluation there are tremendous developments in the last 15 years or so, in fact going back to another 15-20 years within countries like Sweden (Malmo-Lund and Upssala areas and in a few dedicated, clinically oriented, cancer registries like in Dijon (Fr), west of Scotland, Munchen, East Anglia, Yorkshire, Eindhoven, Florence and Torino; they were often the basis of the high resolution studies of Eurocare (starting in 1991) and of the Eunice project from Prof dr H Brenner, starting in 2006..

Generally they were driven by the well known variety of forces of:

- Medical technology and subspecialization: need for more regionalization
  - Emergence of targeted drugs (since about 5-7 years)
  - Surgical awareness of prevention of complications
- Better information technology and accessible databases
  - Emergence of clinical epidemiology also within the various specialties
  - Regional networks in which the registries ‘flourished’
- Demography → more elderly, with also co-morbidity (being an indicator of complexity)
- European grants for comparative studies, bringing clinical scientists together

What happened? On the one hand

- Broad cancer registries, following the example of the aforementioned more clinically oriented ones; following the 2001 Veldhoven IARC workshop\(^1\) – expanded often from the basic use of collecting routine minimal data and in 2012 up to 60% (of the responding 125 of 175 active cancer registries) collecting data on stage at diagnosis and about 50% is active in this field (covering 20-30% of European populations); each covering a wide array of - often the more frequent - cancers

- while on the other hand in the Nordic countries (except Finland) and increasingly also in the northwest of Europe with a southeast gradient multi-hospital based clinical databases (sometimes getting close to being population-based through linkages and connections with the traditional population-based cancer registries) developed and fed by clinical professionals with epidemiology training becoming able to publish interesting papers on short and long term survival, side effects like osteoporosis and suicide risks of cancer patients but on a tumour-specific basis. Often the data collections, sometimes enriched by linkages to other databases developed as if they were supporting randomized clinical trials, but with less intensive surveillance.

- As also appeared from the Eurocourse summit of 2011 and from various presentations at WP 6 workshops both of these developments are gradually merging into European collaborations where approaches of minimal and (too!!) extensive data sets struggle on, until now with insufficient funding and many opportunistic solutions for logistic and methodological problems.

- The workshop aimed to explore the field and see opportunities and challenges from the (manyfold) problems at regional, national and European level. And based on experience and referring to principles of research for quality assurance D 6.3 this is a clinical epidemiological challenge following the principles of research of quality of care: work with good study questions (usually about variation or inequality) with minimal datasets entered into valid databases neutrally led under the aegis of good research and registry governance.

2 WORKSHOP

**Principles, Best Practices, Requirements to Clinical cancer Registries interacting with or part of population-based cancer registries**

**Date:** June 6 – 13.00 to June 7 – 14.00

**Place:** Amsterdam (Schiphol)

**End product:** A deliverable on population-based study methodology, best practices & wide and rapid dissemination

**Co-chairmen:** Valery Lemmens PhD (Eindhoven) (involved in WP 6) and Mats Lambe MD Sweden (member of Steering Board of Eurocourse)

**Aims of the workshop**

Given the rapid developments in
- IT (online/web based),
- patient involvement,
- buyer & market forces,
- increasingly available info about (too?) large variation in care, leading to
- variety of professional initiatives to explore clinical oncological process
  - (incl. staging & utilization) and outcome in a quantitative way,
  - via more – population-based or not – tumour/tract/therapy - specific clinical databases (with often good but temporary funding) either outside or within the domain (or control) of population-based cancer registries.

Contrasting
- earlier reluctance/slowness in participation to Eurocare high resolution studies
- the recent luxury of clinical databases, needing guidance on data protection, IT-solutions

Explore the state of the art in the various memberstates

If general aims are to:
- Be truly comparative with respect to process and outcome, also in elderly but subspecializing as well \( \rightarrow \) regional frameworks needed
  - Thus give short term feedback to providers (of course also long term, but later)
  - Include patient reported outcome (taking into account education/SES)
  - Be multi-disciplinary (include by definition regional pathology & nuclear medicine, radiotherapy facility)
- Then to:
  - be prepared to study short term (complications) and long term toxic side effects (including other sites)
  - Keep datasets as lean as possible (registries can be sampling frame)
  - Interpret & comply with standards of
    - data protection
    - data integrity & neutrality

Realizing that there is much at stake here (good and bad, a.o. fragmentation of registries; Registries suddenly becoming popular and potentially better funded, but also dwindling.)
Program June 6: 12.30: Lunch
(then presentations 15-20 minutes each including discussion of 5 minutes, www.eurocourse.org
13.30 – 15.30: **Block 1:** Overall aims, Nature of the research process, oncological context, methodology and important issues, data-ownership, governance and safety & integrity
- JW Coebergh (NL) 10’– Eurocourse WP 6: issues in population-based clinical evaluation: why we should follow the 20/80 rule? (minimal datasets etc)
- Introduction by co-chairman Valery Lemmens (NL)
  o Clinical databases in oncology: validity & sustainability.
- Key note: Prof. Ewout Steyerberg (NL- Erasmus MC) –
  o Methodological aspects of using clinical databases: precautions warranted.
- M. Iachina (DK)
  o Impact of co-morbidity on survival of patients with non-small cell lung cancer.
- Ron Herings (NL)
  o Pharmaco-epidemiology linked to cancer registration in support of quality assurance of utilization of oncology drugs: requirements to data governance, data safety/integrity.
- Myrthe van Herk (NL)
  o European Examples of pharmaco-epidemiological databases for the study of targeted drug utilization: approaches.
- Mark van Loon (NL)
  o Worries in the back office: possible threats on data safety & integrity in web based data management systems.
- Hans Storm (DK)
  o Ethico-legal implications: use of Eurocourse amended ENCR guidelines (after closure of WP 2 meeting in same hotel) (see deliverable D 2.4).
- All:
  o Need for and experience with linking with radiotherapy: why and how
    - (examples from the UK, emerging, and from Eindhoven, by Vulto et al.).
15.30 – 16.00: Coffee/tea
16.00 – 18.00: **Block 2:** Developments in clinical registries in the various member states (current experience, recent plans and involved stakeholders + relation with population-based cancer registry): sustainability
  Introduction by co-chairman M. Lambe (SE) 5’
  - Sabine Siesling (NL) – NABON breast cancer audit: from where it came.
  - Valery Lemmens (NL) - Strengths & weaknesses of Dutch clinical databases for colorectal cancer (DICA), kidney cancer and haematological malignancies (Pharos) : fact sheets as alternatives.
  - Timo Hakulinen (FI) – Current position and (clinical) perspectives in Finnish Cancer Registry.
  - Josep M. Borras (ESP) – Clinical audits and population based cancer registries in Catalonia.
  - Liesbeth Vaneycken (BE) – Developments in Belgium.
  - Jan Adolffson (SWE) – Clinical and Cancer Register Data - What's in it for me?

Programme June 7 (presentations 15-20 minutes, each including discussion of 5 minutes)
8.30 – 10.30: **Block 3:** Diverse relations relation between clinical databases and population cancer registries
- Arlette Danzon (FR) – Developments in France.
- Alexander Katalinic (GE) – future challenge of connecting population-based and clinical cancer registrations in Germany
- Jutta Engel (GE)– New developments of the German National Cancer Plan and the implementation of area-wide population based clinical cancer registries in Germany.
- Jan Nygård (N) – Developments in Norway: the technical aspects.
- Henrik Moller (UK) – Useful variation in cancer care?
- Gill Lawrence (UK) – The situation of clinical databases & audits in the UK.
10.30 – 11.00: Coffee/tea
11.00 – 12.30: **Block 4:**

**Towards (more) European collaboration: chances, pitfalls and challenges**
- Harry Comber (IR) – Potential of adding quality of care measures to the routine registry data at European level.
- Gemma Gatta (IT) – From Rarecare to specific multinational clinical databases.
- Collette van de Broek (NL) – The Eurecca project; first results and future goals.
- EUNICE-group → EurocanPlatform (WP 11) and EPAAC initiatives for outcome research
- Eurocare VI: in the phase of data-submission-analysis and reporting in 2013
- Paediatric cancer: long term FU (no news)
- Towards a session at ECCO-ESMO 2013: submission of proposals until 17 april 2013
12.30 – 12.45: Summarizing and perspective – JW Coebergh
13.00: Lunch

**Proposal for an (expanding) overview table of Clinical Databases** *(for ERAnet)*

To be used as:
- an appendix in the report and article on perspectives & requirements on clinical databases

**List of**
- In principle population-based or striving to be - clinical oncological registries per country/area with the following features
- Year of start
  - Number of new cases per year
  - Sites/tracts covered (or exclusions)
  - Aim: study questions (global/brief): quality of care and/or prognostic e.g.
    - Data on complications/recurrence/progression/QoL etc?
    - Intensity of Feedback
  - Contact person / www

**Input:**
- Data collection/acquisition/validation: how, by whom, neutral?
- Minimal dataset (accessible at..) (guideline-adherence related?)
- (expanding?) coverage, number of hospitals (community/specialized)
- Explicitly involved/responsible medical specialties
- Automated Methods of data collection? yes/no/how; relation with traditional CR

**Throughput**
- Linkage to cancer registry: ad-hoc, regular, continuously
- Feedback to medical providers: (ir)regular
- Applied methodology/statistical support
- Specific IT arrangements
- Privacy arrangement (informed consent, opt-out)
- Linkage with university departments (methodology, oncological content)

**Output** *(funding for data collection/ assemblage/analysis)*
- Stakeholders (patients, professionals, ’buyers/sellers’)
- Major publications (peer reviewed, reports, provide/updated list)
- Funding arrangements
  - By whom?
  - How much? Per patient?
- Parallel services within normal cancer registry (per tract/tumour) yes/no
3 PERSPECTIVES & REQUIREMENTS FOR SYNERGY BETWEEN POPULATION-BASED AND CLINICAL DATABASES

All in all, this task of Workpackage 6 explored developments in the domain of clinical cancer registries, their potential synergy but also overlap and antagonism with traditional cancer registries as far as also moving into the domain of clinical evaluation. Clinical cancer registries, population-based or not, are popping up everywhere, mostly on a tumour by tumour basis and also driven by modern (and costly) IT, their ‘raison d’être’ consisting of demands of stakeholders, (see also D 1.2.)

- patient groups demanding transparency
- professionals demanding insight in their own practices and of their colleagues, worried or unsurprised about variation in practice or adherence to, often inadequate, guidelines
- both referring general practitioners and specialized doctors and nurses
- given the multi-disciplinarity a complex challenge from medical point of view
- boards of directors of hospitals and other authorities co-responsible for suboptimal working circumstances and capacity development (training and investment in high technologies)
- payers or buyers of health services also demanding value for money
- cancer epidemiologists and biologists seek to use the cohorts assembled also for translational studies of biological determinants of outcome for which (later) a working group of National Cancer Institute (NCI) group developed a research agenda. ²

Interestingly, there is a professional service paradox in the domain of information on cancer services and outcome: in the ideal situation of optimal quality of care delivery all the processes, including training, may have been well planned and programmed and a variety of outcomes would also be documented and communicated with functional IT, preferably after feed back and/or peer review - at loco-regional, national and supranational level. So, the less one needs all this information any more, because care processes and outcomes are already satisfactory and without bureaucracy, the more and better data would be available for even better information (that one hardly needs). Of course it becomes again essential, when registries (have to) monitor the impact of new technologies (e.g. does staging & adjuvant therapies, minimal surgery, hypofractionated radiotherapy, deliberate ‘undertreatment’ in the elderly harm patients? ) and uncertainties on rate of recurrences or long term side-effects dominate. And isn’t it very good to stimulate curiosity also by impressing reading ‘colleagues’ with how good or ‘bad’ one’s performance has been (although they might be aware of publication bias), but what about the use of exhibiting how far patients of other colleagues might still be off from being served by ‘best practice’ unless we all see the health system as a learning exercise.

In reality, it is already widely known that the provision of specialized oncologic care widely varies in and within most member states, with early and late adaptors always being there. As such shortening the lag time is a lofty objective, also contributing to less inequality. However, research processes and publication trajectories of 5-10 years are no exception, as combined registry studies always seem to need, although they are just about systematic observation of current (preferably most recent) oncologic practices and thus serving a learning process rather than being ethically or data protection wise considered experimental clinical research. WP 2 also suggests to facilitate this research.

Those who thus carry professional or managerial responsibility for quality assessment in oncology are however in need of making – often small - steps forward, via investment plans which need underpinning and thus consider ‘good’ or even ‘best’ practices and data on trends and variation, indeed coming from the cancer registry. The EU with its varied mix of member states comes in sight as a living learning experience, in fact the background for an ERA-net project (like EUROCURSE) on improving coordination of –population-based- research of oncologic practice. But although it may strive at funding or having adequate health (care) information for e.g. research and also prevention policy purposes, the data on these activities and their impact or results are generally derived from the –by definition imperfect national or regional -health systems. Can (privacy) strings attached research coincide with an urgent need for openness, indeed by professionals to policy makers and patient groups.

² Elena J. et al. Leveraging epidemiology and clinical studies of cancer outcomes: recommendations and opportunities for translational research . JNCI 2012 (advance Access publication);
Cancer registries definitely have a role here, also for clinical evaluation – in fact it was a reason to start many of the regional registries - already for more than 50-60 years often on the initiative of clinicians often radiotherapists (the latter being true oncologists at the time) who increasingly and since the last 25 years, definitely also stimulated by the ‘Europe against Cancer’ program.

- It is perhaps no surprise that the best functioning oncologic health systems in and within the various member states in 2012 can be found there where strong cancer societies exist but who have developed (trusted, funded and supported by the public), also funded by them
- Moreover, cancer registries have been functioning for quite some time, decades at least without ever violating rules of data protection.
- Policy makers can react underpinned by data (e.g. the Eurocare study being a good example) when ‘things’ have gone wrong (whether it is the high incidence from failing prevention or or the low survival by adequate organization of care or training) for all sorts of political reasons, as the example of the ‘bad’ survival rates of the UK and Denmark has showed.
- Another argument: anno 2012, the various European oncologic journals seem hardly interested any more in accepting for publication such quality of cancer studies just from one area or country or another, while but the more in multi-country /regional studies

The emergence of – often tumour specific - clinical registries can be seen as a sign of heightened clinical professional awareness (because without their initiative they wouldn’t come off the ground) in which the aforementioned stakeholders have great interest. What can be learned so far:

- every country follows a different path in this respect, largely depending on the clinical orientation (is the ‘quality of care’ research domain part of the mission of the traditional epidemiologic, pathologic or statistical orientation of the cancer registry;
- most of these registries widely diverge in their governance concerning input, through-
- international collaboration and standardization in this respect went slowly, not only by the toughness of attaining comparability, standardization etc., but also because of differential perception of loco-regional clinical and policy responsibilities, e.g. the felt need to become comparable with the rest of Europe;
- surprisingly much has still been realized with so little (extra) money for bringing data together, analyzing, giving feedback and publishing (see next chapter 4 for the discussion of the various European comparative and pooled data studies)
- Experience has definitely grown to make the next steps at loco-regional, country and European level, seeing the results of modest funds for data analysis following certain principles

But more synergy is undoubtedly possible based on the following principles: (Recommendations) for an intensified program of quality of care research publications

- Relevant study questions please, no routine monitoring
- Pilot studies
- Minimal datasets forces to restriction to key unequivocal indicators
- Neutrality, professionalism with regard to data input and data processing
- Rapid publication (rather quick and dirty than thorough and ‘mustard after the meal’ in other words stimulating professionals and patient groups in areas where there is ‘nothing’ to come into action
- Good arrangements for linkage to relevant other registries
- A platform of exchange of such outcome studies (annually there are probably more than a hundred relevant studies to order by tract, tumour site and to be disseminated widely.
One could think of platforms to be created by ENCR and Eurocare steering committee and EORTC of specialized epidemiologists (from the Cancer Registries) and rep’s from the various clinical disciplines, radiotherapists, pathologists and radiologists being always involved concerning (rare) cancer of the

- Head and neck
- GI system
- Upper GI
- Hepatobiliary
- Lower GI
- Respiratory
- Skin (Melanoma, SCC, BCC)
- Central nervous system
- Breast
- Female genital
- Male Genital
- Uropoetic
- Bone & Sarcomas
- Haematopoetic
  - lymphoma
  - Leukemia
  - Myeloma
- Endocrine : thyroid
- Uncommon cancers which concern more sites
- Childhood cancers
  - Haematopoetic
  - Blastomas
  - CNS tumours

To summarize and communicate the population-base articles/reports for each of these tracts/tumour sites would be a very fruitful exercise. The degree to which this is attained the coming 5 years should determine the structure and synergy whereby both methodology and costs go hand in hand for sustainability and following principles of Governance.
### Table 1: Spectrum of population-based and clinical cancer registries in Europe: major features, dynamics, pitfalls, involvement of research domains, specific tumor groupings, linkages to cohorts and potential for European studies anno 2012

<table>
<thead>
<tr>
<th>Major Features (Eurocourse WP#)</th>
<th>Traditional cancer registry: incidence/survival</th>
<th>Traditional cancer registry: also with stage</th>
<th>Traditional cancer registry: Clinically extended (for selection of cancers)</th>
<th>Clinical cancer registry /audit: tumour/patient-based</th>
<th>Clinical cancer registry: audit/ Intervention ##/based</th>
<th>Major Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage (3)</td>
<td>Regional/national</td>
<td>Mostly Regional</td>
<td>Regional/National</td>
<td>Regional/national</td>
<td>diversity</td>
<td></td>
</tr>
<tr>
<td>Follow-up (6)</td>
<td>Passive→active</td>
<td>Active</td>
<td>Active ??</td>
<td>Active</td>
<td>Complex &amp; crucial</td>
<td></td>
</tr>
<tr>
<td>Data protection (2)</td>
<td>EU-directive 1995</td>
<td>Idem</td>
<td>Idem</td>
<td>Idem</td>
<td>Anno 2012-13 in a flux</td>
<td></td>
</tr>
<tr>
<td>Data integrity: (3,6)</td>
<td>Paper→electronic Data managers</td>
<td>Idem</td>
<td>Also web-based</td>
<td>Mostly web-based</td>
<td>Dynamic &amp; instable</td>
<td></td>
</tr>
<tr>
<td>Validity (6)</td>
<td>- Internal - external</td>
<td>Data managers</td>
<td>Data managers</td>
<td>DM &amp; Care Providers Evolves in RCT-dataset</td>
<td>Neutrality Consistency !!</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal dataset</td>
<td>Extended minimal dataset</td>
<td>Care Providers /data managers → cave RCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiative: (1)</td>
<td>Public Health /Oncology</td>
<td>Oncology/Public Health</td>
<td>Oncology/PH</td>
<td>Government/industry/ Oncology/payers</td>
<td>History affects culture</td>
<td></td>
</tr>
<tr>
<td>Governance: (1)</td>
<td>PH/Oncology/Cancer society</td>
<td>Oncology/PH/Buyers/cancer society</td>
<td>Professionals/Buyers/gov’t</td>
<td>Govt/Industry/private</td>
<td>Implicit &amp; shifting</td>
<td></td>
</tr>
<tr>
<td>Clinical involvement (6,8, 9)</td>
<td>X</td>
<td>Xx</td>
<td>Xxx</td>
<td>Xxx</td>
<td>xxx</td>
<td>Increasing</td>
</tr>
<tr>
<td>Patient involvement</td>
<td>Little</td>
<td>Little</td>
<td>Towards transparency</td>
<td>Towards transparency</td>
<td>Idem ??</td>
<td>Publication</td>
</tr>
<tr>
<td>Academic affiliation</td>
<td>x</td>
<td>x</td>
<td>xxx</td>
<td>xx</td>
<td>xx</td>
<td>Publication</td>
</tr>
<tr>
<td>Research domains (nr involved)</td>
<td>1-2</td>
<td>2-3</td>
<td>3-5</td>
<td>Clinical + PRO 1-2</td>
<td>1-2</td>
<td>Variety</td>
</tr>
<tr>
<td>1a. Public health: frequency, etiology</td>
<td>Xx</td>
<td>xx</td>
<td>Xx</td>
<td>x</td>
<td>x</td>
<td>Comparability</td>
</tr>
<tr>
<td>1b. Public Health: screening (5)</td>
<td>X</td>
<td>XXX</td>
<td>XXX</td>
<td>x</td>
<td>XXX</td>
<td>Underestimated importance</td>
</tr>
<tr>
<td>2. Quality of care 6</td>
<td>X</td>
<td>Xx</td>
<td>XXX</td>
<td>XXX</td>
<td>??</td>
<td>Expanding</td>
</tr>
<tr>
<td>3. Survivorship (6)</td>
<td>X</td>
<td>X</td>
<td>XX</td>
<td>X</td>
<td>X</td>
<td>Expanding</td>
</tr>
<tr>
<td>4. Prognosis (6,7)</td>
<td>X</td>
<td>xx</td>
<td>XXX</td>
<td>XX</td>
<td>xx</td>
<td>Serving TR</td>
</tr>
<tr>
<td>Specific group-ings: (6)</td>
<td>Tumour/tract</td>
<td>Age + Tumour-specific</td>
<td>Multi-tumour-specific</td>
<td>Variety</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>-----------------------</td>
<td>-----------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare cancer Childhood cancer</td>
<td>Xxx Xx xxx xxxx Xxx</td>
<td>Xx xxx ??</td>
<td>EU-directive late effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple cancer</td>
<td>Xxx xxx xxx --- ---</td>
<td>--- ---</td>
<td>Growing problem</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Linkages to (2,3) cohorts/databases**

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>D: min CoD: ??</th>
<th>Idem</th>
<th>Diverse</th>
<th>Depending on MS</th>
<th>Diverse</th>
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<tbody>
<tr>
<td>Pathology (6,7)</td>
<td>Diverse</td>
<td>Diverse</td>
<td>Often</td>
<td>Often</td>
<td>Diverse</td>
</tr>
<tr>
<td>Biobanks (7)</td>
<td>X</td>
<td>Xx</td>
<td>Xxx</td>
<td>xx??</td>
<td>Molecular</td>
</tr>
<tr>
<td>Hospital discharge (3)</td>
<td>Diverse</td>
<td>Diverse</td>
<td>Often</td>
<td>Often</td>
<td>?? Quality ?</td>
</tr>
<tr>
<td>Screening (5)</td>
<td>X</td>
<td>xx</td>
<td>xx</td>
<td>??</td>
<td>Very important</td>
</tr>
<tr>
<td>Determinants of risk</td>
<td>xxx</td>
<td>xxx</td>
<td>??</td>
<td>??</td>
<td>Essential</td>
</tr>
</tbody>
</table>

**European studies (4)**

<table>
<thead>
<tr>
<th>Pooled database (2)</th>
<th>x</th>
<th>x</th>
<th>Xxx (Rare cancers)</th>
<th>??</th>
<th>??</th>
</tr>
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<tbody>
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<td>Comparative study</td>
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X = feasible  xx = relevant xxx = essential (= relevant + unique)  # workpackage number of Eurocourse  ## includes Radiotherapy, Drugs, endoscopy

??: depends on study question, given questionable comparability due to unequal studybase (unless to be considered as work in progress)

PH: public health, MS: Member States TR = translational Research

---

3 Tumour and tract specific cancer registries, especially in Italy and France (e.g. Dijon)

4 Breast, cervix, colon (and research on prostate, lung)
### Table 2 Inventory of clinical registries (made in autumn 2012; to be refined)

- x = planned/just starting, xx = running < 5 years, xxx= running for 5+ years; P= population-based; B= linked to biobank

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Abbreviations /footnote

HR = high resolution
J: 75 clinical cancer registries planned
Remarks:  K: Testicular cancer: P (administrative data bases linked with the cancer registry, quality of care)
L: no registers to include in this list
M: clinical & biological multi-centric databases started in 2011 + tumour banks with Canceropole
N: Unique role of Dijon: 3 major clinical registries
O: 75 clinical cancer registries planned
P: unique situation in Europe
Q: Rarecarenet; information network
R: was a traditional clinical registry
S: Registries of referrals to and in population-based radiotherapy centres e.g. at: Eindhoven, Tilburg, Arnhem, Enschede, Leeuwarden, Den Haag/Delft: (independent data input) by CRs(IKZ –coordinating & IKNL)
T: increasingly fragmented & chaotic with much overlap & competing funding and competence
U: Also registry of solid tumors in children: from jan 2002, n=1600, no follow up
VoC: variation in care
V: P (integrated cancer registry, variation in care for solid tumors in children
W: Also national registers for penile and testicular cancer
Y: Projects for specific years only. Audit planned for 2011 patients: Lung, Breast, Colorectal and Prostate. Data from Multi Disciplinary Team meetings for all cancer sites; routine downloads possible
4 EUROPEAN COMPARATIVE STUDIES OF SURVIVAL

Comment on European Comparative studies of survival being the only indicator EUROCARE experience with comparative European high resolution studies

4.1 Studies of relative survival

The high/low resolution studies were a wonderful i.e. ‘avant la lettre’ initiative by dr Berrino and his team at the divison of Clinical Epidemiology of the National Cancer Institute in Milano soon after the start of the European Concerted Action on Survival and Care of Cancer Patients (EUROCARE). Already since 1990 the protocols were written for studies of stage-related determinants of survival of breast, colorectal and prostate cancer; they were soon followed by stomach and testicular cancer and after 2000 again for breast and colorectal cancer. Aspects of staging were also explored through the availability of imaging and/or diagnostic activities of surgeons (exploration and excision of lymph node nodes and explorations by pathologists of excised lymph nodes). But even something simple proved complex at the time for many registries: first of all, the readiness and capacity to collaborate was modest. Of the gradually increasing number of participating registries in Eurocare less than 25-33% did, but most had difficulties to obtain extra data on staging for a random sample of a few hundred newly diagnosed patients; the argument being lack of resources (there was no European money for data collection, only for data analysis in Milano). One could also argue that it was a lack of ‘true’ surgical and pathological involvement in the registry process as a means to improve oncologic care for future patients. Somehow it was perceived too much as a burden to the registry instead of a challenge of being enabled to compare staging and treatment performance with those of others. All in all this not only led to a modest response for participation (by only 10-15 registries), but also the publication dates extended in time often being 5-9 years after diagnosis. Always the middle European registries (Slovakia, Poland) and the UK and Denmark ending at the lower end of any league table and France with its exuberant access to oncologic diagnostic services and surveillance on top, with however relatively many overdiagnosed cases.

In other words: the opportunity offered by the dedicated Italian researchers was not fully grabbed until about 2005. This may however have changed since about 7 years or so when the idea of clinical registries and audits (largely became gradually stronger within especially the nordic countries and ESSO (Eur Society of Surgical Oncology). That will also provide the trigger for funding opportunities from the EU, although with clear limitations. If one considers such research activities as quality assurance, but done scientifically, then the EU might rather be interested in providing and supporting the framework for protocol development, data cleaning, analysis and dissemination, but the memberstates should, either at national of regional level, fund the data collection, provided the protocols are good (‘sharp’ study questions, good possibilities to interpret the data) and rapid performance and publication.

If the rationale of such studies is to show variation in care provision and outcome to doctors and clinical scientists, then both ‘good’ and less good areas are needed, so that the ‘good example is then also the perspective not only for the bad but even more for areas with non-existent data whatever the reason. Patients might be much worse off there, and it may start discussion to do something about that. Patient groups might be alerted. In fact the responsibility for any imaginary program owner.
RECOMMENDATIONS on European studies

The principle of these population-based ‘resolution’ studies of incident cases should thus be:

- Compare unequivocal elements of quality with great flexibility
  - maximum of about 100 € per patient, ranging thus from 50 – 150 € across the EU (50-75% for data collection, 25-50% for data analysis and dissemination)
- Should be done quick (and dirty), following the 20-80% rule.
  - Not striving for the perfect information, because it will always evolve
  - Discussion with experts will add its own dynamics
- Aiming at those who need to get started, especially where there is ‘nothing’.
  - where patients are likely to be most at risk for not being adequately staged or treated or get proper surveillance,
  - where probably most variation in care delivery exists, a matter of opaque inequality.

And the EU can contribute here by funding

- protocol development
- data analysis
- co-fund data collection when they are delivered in time (possibly?)
  - publication needs to be within certain time limits, e.g. 2 years.

Such studies usually lead to interesting discussions, especially at congresses within European scientific medical and surgical societies, with controversies on newly developed guidelines or with new clinical trials proposed or announced.

Therefore, it might be very useful to involve prominent members of the various EORTC clinical groups, or from Biomedical Scientific societies like ESMO, ECCO, EHA because they might also be interested to have questions on the dissemination of certain therapies that they are or have been investigating.

Conclusion: the Eurocare resolution studies have been a very good, but slow start, because awareness of its potential impact was for a long time too low at national level, causing low participation and delays. Thus, such comparative activities need to come at a higher level and with more professional interest at both locoregional, national and European level, not the least the European Network of Cancer Registries. A useful coalition can be formed whereby the scientific challenge is rather to limit oneself and gradually expand. As the network of registries of Eurocare and that of ENCR overlap to a very large extent and the Eunice network of dedicated registries has also proven itself since 2008 there might be 4 options for hosting minimal datasets for analysis of process and outcome (survival primarily), assuming that such protocols will largely be developed by content matter professionals + clinical epidemiologists from clinical cancer registries, see D 6.5.

The four options are:

- The traditional Eurocare datacentre in Rome
- Through the new, to be refined for this purpose, WP4 portal at IARC, with logistical support of JRC (Ispra),
- A new option: at the EORTC with their great experience in data management and linked primarily to tumourspecific EORTC study groups
- Datacenter of the Eunice Survival Working Group at the German Cancer Centre (Heidelberg)
There is another reason for the locoregional and possibly national approach, especially in larger countries: the aspect of data protection should not be neglected or, more likely misinterpreted. If we are dealing with quality assessment, attending physicians may allow registry personnel to look into clinical records, thus guaranteeing consistency, neutrality and external validity of the collected data really needed for comparative quality assessment. Given the changes in the legal landscape quality assessment sooner or later may either become easier and nobody seems to be harmed has also legal consequences as affected by its implication on current and future patients; with regard to data protection it falls under the hippocratic oath and can be arranged under a regime being generally informed at hospital level with possibility to ‘opt-out’, but clearly distinct from the more extensive data collection efforts for clinical trials for which informed consent is needed. Whether data from automated records or written clinical records does not matter. The more data would need to be collected from clinical records, the more it resembles a clinical trial. Also in quality assurance there need to be clear study/research questions but more of an exploratory character.

EUROCARE HIGH RESOLUTION ARTICLES (from recent to old)


Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gatta G, Capocaccia R, Sant M, Bell CM, Coebergh JW, Damhus RA, Faivre J, Martinez-


European-American comparisons with EUROCare

Data of the resolution studies can also be used for all kinds of international comparisons. Below the experience so far.


Other European American comparisons of survival from EUNICE project

Since 2007 a network of 10-12 dedicated cancer registries has been founded for advancing methodology in survival analysis by Prof Brenner at the German Cancer Center and expansion might be possible. As seen from the papers the contributing authors come from all over Europe. Below comparative studies with the USA.


4.2 European studies of Rarecare

Comments

Uncommon cancers always speak to imagination of young and experienced doctors because they are unusually interesting, often only described in case studies. As indicators of risk and prognosis incidence and survival and prevalence fulfil basic requirements. Interest for rare cancers increased in the last 25 years from four different viewpoints:

- The shifting need to subclassify cancers with better immunological, endocrinological, biochemical, cytogenetic or molecular methods or specific modes of imaging techniques often requiring specific expertise in centres
- Illustration of the need for taking part in national or international networks and often also leading to consultation of subspecialised doctors or concentration of care
- Changes in the domain of regulation of Orphane drug development since 1999, which allows pharmaceutical companies a longer period for their patents in case the prevalence of the cancer condition would be <5 per 10,000.(EU directive EC 141/2000)
- Emergence of the Cochrane Collaboration in the domain of guideline development in the late 80’s discovering an area which needed to be filled by a special handbook in the absence of guidelines

Although cancer registries should be ideal vehicles for describing incidence and survival of uncommon or rare cancers, such reporting has remained sparse. In Europe EUROCIM, the combined database of the cancer registries in the 90’s was only partly filling the space at IARC without being used very much by the registries. Nor were ll disease entities defined. After a publication from the SEER-program in 1995, the Eindhoven Cancer Registry also produced data on incidence and prognosis of a large number of uncommon tumours at most sites following criteria of uncommonness, both histology and site: non-cutaneous melanomas, extra-nodal lymphomas, non extremity located sarcomas, carcinoid and germ cell tumours in adults, unusual histologies like small cell tumours outside the lung and/or locations.

The quality of the histological data is obviously crucial and depends on the pathologists and those who commission their services, the surgeons (also including gynaecologists and urologists) and the way they are embedded in multi-disciplinary activities. A problem without a good solution is that rare cancers can be part of a wider spectre of premalignant or benign conditions, especially in tumours of the brain or of endocrine glands or tissue.

Since 2003 quite a few approaches were followed, gradually resulting into the RareCare project, funded by DG Sanco, concerning the registries that besides participating in the EUROCIM database (WP4, under construction [http://eco.iarc.fr/EUROCIM/Default.aspx](http://eco.iarc.fr/EUROCIM/Default.aspx)) of the European Network of Cancer Registries (ENC) had already pooled their data within the Eurocare database. Surveillance of Rare Cancers in Europe (RARECARE) comprised 89 population-based cancer registries (CRs) in up to 21 European countries, serving patients newly diagnosed between 1978 and 2000.

The Rarecare overview paper (12), estimate that about 20% of all cancers fall in the category Rare, partly thanks to the cut-off point of the incidence rate of 6 per 100,000 person-years. Moreover, 5-year survival rates of patients with rare cancers were 46 % versus 65% for patients with non-rare cancers. All together, there might be about 4,300,000 (ex?) patients with former Rare cancers in Europe based on a total incidence rate of 108 per 100,000 person years. In each or the 11 tumour specific papers specific considerations have been proposed for adaptations or improvements.

Working with this database and the literature, the self-appointed RARECARE working group produced a new list of cancers, adapting the definition of rare cancers ([http://www.rarecare.eu](http://www.rarecare.eu)) which was ultimately based on a prevalence of 50/100,000.

**Further remarks and pitfalls**

**What to do when ……**

- the indicator of incidence varies across the EU and over time, so that it would qualify as rare in some member states but not in others: e.g. testicular or cervical cancer might vary from 4 to 12 per 100,000,
- the indicator of survival may also vary a lot by either late detection or wider inclusion of pre- or non-malignant histotypes, e.g. endocrinological tumours or brain tumours. A European average may not make any sense.

And definitions also matter here for in- or exclusion of certain entities, e.g. the current four histological types of melanoma can be divided in a bad prognosis- low incidence and prevalence group of nodular and acral, thicker melanomas and a favourable prognosis high incidence superficial spreading and lentigo maligna group of thin melanomas on the other hand. The former more often needs the new immune-stimulating targeted drugs are rather prescribed to patients with the former rather than for the latter. Understandably, such a discussion may have far reaching financial and other consequences, e.g. also putting centralization of oncology in the spotlight and the need for assessing its effectiveness.

As of 2012 besides the mentioned European publications (see page…) many national papers are currently appearing in press, provoking much discussion and likely used in:

- emerging plans for improvement of care at regional/national level, raising awareness among surgeons often by exploring variation in diagnosis and treatment
- actualization of the data set through Eurocare but also through explorations of new disease entities and clustering in EUROCIM;
- Eurocare might be fed through Eurocim if there are specific quality controls.
- expansion of the scope of existing or starting new specific registries with greater emphasis on benign affiliated conditions
- bringing together the various national study groups in European groups with ideas for research projects for the 8th framework
- Plans for optimizing secondary use of tissue through the various pathology laboratories or start new biobanks.

**Conclusion**

Combining data from cancer registries for risk assessment and surveillance of patients with rare cancers to study an imaginary epidemic and improve their care has clearly become ‘en vogue’ since 2000 extending in the near future, not only in the age of molecular medicine and targeted drugs, but also for timely recognition of unusual clinical situations.
Although the Rarecare project has not been extensively discussed within Eurocourse (conceived in 2007), because it did only deliver in 2012 and did not fit specifically in a workpackage, this might have been WP 3 (classification), 4 (portal), 6 and 7 (biobank) and of course 8 and 9 as a disseminating good practice. But also in WP 2, because with such patients there is much exchange of data and they might easily become identifiable and thus need very large datasets. It is quite clear that the pooled data derived from patients diagnosed between 1978 and 2000 contributed to epidemiological insight (every epidemic always starts small) and quality of cancer care and that a more recent period of diagnosis and more registries being involved will improve this insight further, certainly if secondary use of the pathologic data can be made. Whether indeed oncologic care of all these patients (more than 20% of all new patients) needs to be centralized or that other ways of knowledge based care guide us to the future, remains to be seen.

**Overviews of population-based studies of patients with Rare Cancer in Europe: incidence, survival and prevalence as indicators for evaluating cancer care**


