KCE REPORT 219

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ORGANISATION OF CARE FOR ADULTS WITH A RARE OR COMPLEX CANCER

KCE REPORT 219
HEALTH SERVICES RESEARCH

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

ORGANISATION OF CARE FOR ADULTS WITH A RARE OR COMPLEX CANCER

SABINE STORDEUR, FRANCE VRIJENS, KRIS HENAU, VIKI SCHILLEMANS, CINDY DE GENDT, ROOS LEROY

COLOPHON

Title:	Organisation of care for adults with a rare or complex cancer
Authors:	Sabine Stordeur (KCE), France Vrijens (KCE), Kris Henau (Stichting Kankerregister), Viki Schillemans (Stichting Kankerregister), Cindy De Gendt (Stichting Kankerregister), Roos Leroy (KCE)
Project coordinator and senior supervisor:	Sabine Stordeur (KCE)
Reviewers:	Marijke Eyssen (KCE), Frank Hulstaert (KCE), Raf Mertens (KCE), Leen Verleye (KCE)
External experts:	**Coordinators of the working groups:** Frederic Amant (UZ Leuven), Ahmad Awada (Institut Jules Bordet, Bruxelles), Ivan Borbath (Cliniques universitaires Saint-Luc, Bruxelles), Tom Boterberg (UZ Gent), Lieve Brochez (UZ Gent), Dominique Bron (Institut Jules Bordet, Bruxelles), Giuseppe Costante (Institut Jules Bordet, Bruxelles), Karen Geboes (UZ Gent), Marc Hamoir (Cliniques universitaires Saint-Luc, Bruxelles), Alex Kartheuser (Cliniques universitaires Saint-Luc, Bruxelles), Jan Lerut (Cliniques universitaires Saint-Luc, Bruxelles), Toni Lerut (UZ Leuven), Philippe Nafteux (UZ Leuven), Eric Van Cutsem (UZ Leuven), Jan Van Meerbeeck (UZ Antwerpen), Ignace Vergote (UZ Leuven) **Pathologists:** Ruth Achten (U Hasselt), Noella Blétard (CHU Liège), Kristof Cokelaere (Jan Yperman Ziekenhuis, Ieper), Cecile Colpaert (GZA, Antwerpen), Romaric Croes (St Blasius Ziekenhuis, Dendermonde - Da Vinci), Claude Cuvelier (UZ Gent), Pieter Demetter (Hôpital Erasme – ULB), Paul Goddeeris (Stichting Kankerregister), Anne Jouret-Mourin (Cliniques Universitaires Saint-Luc, Bruxelles), Eugène Mutijima (CHU Liège), Michel Pétein (Institut de Pathologie et de Génétique, Gosselies), Isabelle Salmon (Hôpital Erasme - ULB), Raf Sciot (UZ Leuven), Thomas Tousseyn (UZ Leuven), Peter Vermeulen (GZA), Wim Waelput (UZ Brussel)
Stakeholders:	Yves Benoit (UZ Gent), Michaël Callens (Christelijke Mutualiteiten), Jean-Jacques Cassiman (UZ Leuven), Donald Claeys (Collegium Chirurgicum Belgicum), Claudio Colantoni (Cabinet de Laurette Onkelinx), Véronique De Graeve (Zelfhulpgroep NET & MEN kanker), Ellen De Wandeler (KankerCentrum), Patrick Galloo (Mutualités Socialistes), Geneviève Haucotte (INAMI/RIZIV), Lore Lapeire (UZ Gent), Lia Le Roy (Werkgroep hersentumoren), Liesbeth Lenaerts (KankerCentrum), Johan Pauwels (Zorgnet Vlaanderen), Marc Peeters (College voor Oncologie), Bruce Poppe (UZ Gent), Ward Rommel (Vlaamse Liga tegen Kanker), Karin Rondia (Fondation contre le cancer), Betty Ryckaert (Werkgroep hersentumoren), Anne Uyttebroeck (UZ Leuven), Simon Van Belle (UZ Gent), Saskia Van den Bogaert (FOD Volksgezondheid/SPF Santé publique), Marc Van den Bulcke (Kankercentrum), Robert Van den Oever (Christelijke Mutualiteit), Elisabeth Van Eycken (Stichting KankerRegister), Wim Waelput (UZ Brussel), Patrick Waterbley (FOD Volksgezondheid/SPF Santé publique)
External validators:	Jeanne-Marie Bréchot (Institut National du Cancer, Paris, France), Pascal Garel (HOPE, European Hospital and Healthcare Federation, Brussel, België), Jan Maarten van den Berg (IGZ, Inspectie voor de Gezondheidszorg, Utrecht, Nederland)

Acknowledgements: Daniel Bodart (INAMI/RIZIV), Piet Calcoen (DKV), Mickaël Daubie (INAMI/RIZIV), Gemma Gatta (RARECARE), Kirsten Holdt Henningsen (KCE), Daphne Hompes (UZ Leuven), Henk Hummel (Integraal Kankercentrum Nederland, IKNL), Marlies Jansen-Landheer (Integraal Kankercentrum Nederland, IKNL), Frédérique Nowak (Institut National du Cancer, France), Helene Probst (Danish Health and Medicines Authority (Sundhedsstyrelsen), Denmark), Sabine Siesling (Integraal Kankercentrum Nederland, IKNL), Bertrand Tombal (Cliniques Universitaires Saint-Luc), Annalisa Trama (RARECARE), Christel Van Campenhout (WIV/ISP), Philippe Van de Walle (WIV/ISP), Nicole Vanlaethem (BELAC), Marcel Verheij (Stichting Oncologische Samenwerking, Nederland), Leen Verleye (KCE)

Reported interests: Owner of intellectual property rights (patent, product developer, copyrights, trademarks, etc.): Marc Van den Bulcke

Participation in scientific or experimental research as an initiator, principal investigator or researcher: Jan Lerut

Grants, fees or funds for a member of staff or another form of compensation for the execution of research: Dominique Bron (ALGENE, JANSSEN, GSK), Lore Lapeire

Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Johan Pauwels, Wim Waelput

Payments to lecture, training remuneration, subsidised travel or payment for participation at a conference: Ahmad Awada, Jean-Jacques Cassiman, Karen Geboes, Lore Lapeire, Jan Lerut, Jan Van Meerbeeck, Elisabeth Van Eycken

Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Jean-Jacques Cassiman (Vlaamse Liga tegen Kanker), Donald Claeys (Collegium Chirurgicum Belgicum), Claudio Colantoni (Representative of Cabinet Onkelinx), Romaric Croes (St Blasius Dendermonde - Da Vinci; Member of Commissie Pathologische Anatomie; CEO/Owner of Fresco Automation & IT Consultancy), Véronique De Graeve (Zelfhulpgroep NET & MEN kanker), Pieter Demetter (Head of Clinical digestive Pathology at Hôpital Erasme), Marc Hamoir (Secretary of the FNRS group “tête et cou”, Member of board of directors of Fondation contre le Cancer), Anne Jouret-Mourin (Chief of pathology service at Cliniques universitaires Saint-Luc), Johan Pauwels (Representative of Zorgnet Vlaanderen), Bruce Poppe (UZ Gent – Universiteit Gent), Betty Ryckaert (Vice-President of Werkgroep hersentumoren), Robert Van den Oever (Landsbond Christelijke Mutualiteit), Wim Waelput (Co-founder of Pathomation bvba), Patrick Waterbley (Director and administrator of H-Hart Ziekenhuis, Roeselare-Menen vzw)

Further, it should be noted that all experts and stakeholders, as well as the validators consulted within this report were selected because of their expertise in the field of oncology. Therefore, by definition, all consulted experts, stakeholders and validators have a certain degree of conflict of interest to the main topic of this report.

Layout: Ine Verhulst

Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**
Publication date:	10 February 2014
Domain:	Health Services Research (HSR)
MeSH:	Rare diseases; Oncology Service, Hospital; Cancer Care Facilities; Centralized Hospital Services; Referral and Consultation
NLM Classification:	QZ23-24
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2014/10.273/21
Copyright:	KCE reports are published under a “by/nc/nd” Creative Commons Licence http://kce.fgov.be/content/about-copyrights-for-kce-reports. 
How to refer to this document?	Stordeur S, Vrijens F, Henau K, Schillemans V, De Gendt C, Leroy R. Organisation of care for adults with a rare or complex cancer. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2014. KCE Reports 219. D/2014/10.273/21. This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AR	Arrêté Royal
BCR	Belgian Cancer Registry
COM	Consultation Oncologique Multidisciplinaire (Multidisciplinary Team Meeting)
EC	European Commission
ERN	European Reference Networks
GP	General Practitioner
HIPEC	Hyperthermic IntraPeritoneal Chemotherapy
HPV	Human Papilloma Virus
IMA	InterMutualistic Agency
INAMI	Institut National d'Assurance Maladie Invalidité (NIHDI)
ISP	Institut scientifique de Santé Publique
KB	Koninklijk Besluit
MKG	Minimale Klinische Gegevens
MOC	Multidisciplinair Oncologische Consult (Multidisciplinary Team Meeting)
NET	Neuroendocrine tumour
NIHDI	National Institute for Health and Disability Insurance
RCM	Résumé Clinique Minimum
RD	Royal Decree
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (NIHDI)
SONCOS	Stichting Oncologische Samenwerking (Foundation of Oncological Collaboration)
TNM	Tumour, Node, Metastasis
VLK	Vlaamse Liga tegen Kanker
WIV	Wetenschappelijk Instituut Volksgezondheid

SCIENTIFIC REPORT

1 OBJECTIVES, SCOPE AND STRUCTURE OF THIS REPORT

1.1 Initiator and objectives

In March 2008, the first National Cancer Plan 2008-2010 was launched in Belgium.[1] Its objective was to reduce cancer-related mortality and morbidity and to improve quality of life of cancer patients and their families. Thirty-two concrete measures in the domains of prevention, treatment and research were listed and translated into 62 specific actions. Since 2010, the Plan was prolonged and additional measures were progressively adopted.[2]

Under the subheading 'Care, treatment and support of the patient', action 13 specifically relates to the care and treatment of patients with rare cancers, aiming to define qualitative and quantitative criteria for their treatment. Besides rare cancers, action 13 focuses also on cancers (rare and common) that require complex care, e.g. complex diagnostic and therapeutic procedures carried out by highly skilled and experienced healthcare providers.[3]

The KCE is specifically commissioned by The Minister of Health and Social Affairs to perform a study with the following objectives:

1. to establish the threshold to define rare cancers in Belgium,
2. to define the competences required to manage patients with rare cancers,
3. to propose a scenario for the organisation of care for patients with rare cancers and cancers that require complex care, taking into account the current Belgian situation and relevant foreign experiences.

1.2 Scope of this report

The scope of this report is the **organisation of care for adults** having a rare cancer or a cancer requiring complex care. In this report, **a rare cancer** is defined as a cancer which affects less than 6 new patients/100 000 inhabitants/year. This threshold is based on a European definition (RARECARE),[4] and corresponds in Belgium to 530 new cases per year.

A cancer requiring complex care is defined as

- A cancer on a very specific and extremely difficult to reach anatomic localisation (for instance a brain tumour or an ocular tumour),
- A cancer occurring during a specific condition (for instance a cancer occurring during pregnancy),
- A cancer requiring a high level of expertise, because of its diagnosis and/or treatment (for instance soft tissue sarcoma, oesophageal cancer),
- A cancer requiring very high-tech or costly technical infrastructure (for instance HIPEC treatment for tumours of the peritoneum).

Obviously, some tumours can be classified into several categories.

The present report does focus on adults facing cancer, as the organisation of care for children with cancer has already been addressed in the soon to be published Royal Decree on haemato-oncology for children (0-15 years old).

1.3 Structure of this report

The first part of this report presents a description of the actual situation in Belgium. Chapter 2 points the similarities and differences between rare diseases and rare cancers and discusses the organisation of care from the patient's perspective. Chapter 3 details the burden of rare cancers (incidence, survival) while the current organisation of care in oncology is depicted in chapter 4. The first part of this report ends with the illustration of the dispersion of care in Belgium and its potential consequences on the quality of care and patients outcomes (chapter 5).

The second part focuses on the international organisation of rare cancers and recommendations to improve the management of patients with rare cancers. Lessons learnt from some European Member States are detailed and the many European initiatives, specific to rare cancers, are described. Criteria proposed at a European level and examples from abroad are exhaustively listed (chapter 6).

The third part is the core of the report: the organisation of care around reference centres in Belgium, and the specification of minimal requirements for the management of patients with rare or complex cancers (chapter 7). After an extensive consultation of stakeholders and clinicians, a proposal for the organisation of care for specific cancer groups is formulated for Belgium (chapter 8). Concrete recommendations can be found in the Synthesis of this study, which is published as a separate document on our website. It can be accessed from the same referral page as the current document.

2 SIMILARITIES AND DIFFERENCES BETWEEN RARE CANCERS AND RARE DISEASES

2.1 Rare diseases and rare cancers: epidemiology, diagnosis and treatment

Rare cancers are at the crossroads of two worlds - the world of cancers and the world of rare diseases. Many issues faced in the organisation of care for rare cancer patients are also identified in the organisation of care for patients with rare diseases: small number of patients, scarcity of expertise, few resources, delay in diagnosis, lack of scientific research and information, insufficient access to care and challenges to develop innovative therapies.[5]

2.1.1 Prevalence and Incidence

Rare diseases are defined as diseases with a prevalence of less than 50 per 100 000 inhabitants. In Belgium there are an estimated 60 000 to 100 000 people (which corresponds to 0.57 to 0.95% of the total population) who need special care because they suffer from a **rare disease**.[6] So far, between 6 000 and 8 000 distinct rare diseases have been identified, including genetic disorders (which count for about 80% of rare diseases), autoimmune diseases, congenital deformities, toxic and infectious diseases and also rare cancers.[6]

The prevalence criterion for rare diseases (i.e. <50/100 000) has also been applied to **rare cancers**,[7] but this approach has serious drawbacks. Some cancers with low incidence and good survival, like squamous cell carcinoma of the uterine cervix and thyroid carcinoma, will not be considered rare since good survival pushes up prevalence data. On the other hand, some more prevalent cancers with poor prognosis (e.g. stomach adenocarcinoma, lung squamous cell carcinoma, poorly differentiated endocrine carcinomas of the lung) are categorised as rare because poor survival pushes prevalence down. These considerations suggest that incidence is a better indicator for rare cancers and also mirrors well the sub-acute clinical course of most rare cancers.[4]

The project Surveillance of Rare Cancers in Europe (RARECARE) suggested to establish the rarity threshold at an incidence lower than 6 new cases per 100 000 inhabitants per year, corresponding to <30 000 new cases per year in Europe. Based on this definition, 186 cancers were assigned the label 'rare cancer',[8] including rare adult solid tumours and rare haematological cancers as well as all childhood cancers.[9] The estimated annual incidence rate of all rare cancers in Europe is about 108 per 100 000, corresponding to 541 000 new cases annually or 22% of all cancer diagnoses. In 2011, about 4 300 000 inhabitants of Europe were living with the diagnosis of a rare cancer, which corresponds to 24% of the total cancer prevalence.[4]

2.1.2 Diagnosis

2.1.2.1 Rare diseases

Most rare diseases are caused by **genetic mutations or variations** (e.g. cystic fibrosis, Huntington's disease, muscular dystrophies). Environmental factors, such as diet, smoking, or exposure to chemicals, can also play a role in the onset of rare diseases, either by causing the disease directly, either by interacting with genetic factors which may cause or increase the severity of disease. Other rare diseases are caused by infection with a pathogen, such as prions (e.g. Creutzfeldt-Jakob disease). Still, for many rare diseases, the exact cause remains unknown.

The diagnosis is firstly based **on symptoms** which may be non-specific or shared with more common diseases. Secondly, **genetic tests** look for alterations in genes or changes in the level or structure of key proteins coded for by specific genes. Today, over 2 000 different tests are available to detect mutations associated with genetic diseases. Many of these genetic tests are offered by just a few laboratories. In Belgium, **Centres for Human Genetics** already play an important role in the diagnosis of rare diseases and provide a state-of-the-art genetic consultation.[6]

2.1.2.2 Rare cancers

After a suspicion of cancer, pathological diagnosis is the gold standard to confirm the presence of a malignancy, and to define the type of cancer and its classification. Pathology sets the foundation for effective cancer treatment. However, many pathologists may be confronted with a specific rare cancer perhaps once or twice in their entire professional career. This is why diagnosing rare cancers accurately can present a real challenge for a pathologist. At the same time, it is extremely important, especially in the field of rare cancers, to combine information from biology, pathology and clinical practice allowing a multidisciplinary team to set up an appropriate treatment plan.[10]

Pathologists need to be aware of the potential diagnostic pitfalls in rare cancer pathology, especially when taking into account that these pitfalls may lead in some cases to inadequate treatment or, worse, to harmful therapy. Eventually misdiagnoses may result in a reduced chance for remission for the patient. Therefore, **second opinions** in diagnostic pathology are more and more required by pathologists to reduce misdiagnoses or to enhance institutional performance improvement plans.[11]

2.1.3 Treatment

2.1.3.1 Rare diseases

As the diagnosis of rare diseases is difficult, many patients may remain undiagnosed and hence not treated. But even when a rare disease is recognised, thousands of patients cannot be treated because no therapies or drugs are available.[3] Often, rare diseases are treated by products labelled 'orphan drugs'. In Europe, orphan drugs first have to obtain an Orphan Designation. This is a legal procedure that allows for the designation of a medicinal substance with therapeutic potential for a rare disease, before its first administration in humans or during its clinical development. The exact therapeutic indication is then defined at the time of marketing authorisation. This procedure has been established by Regulation (EC) No 141/2000.[12] Although the EU approved more than 60 orphan drugs and assigned more than 600 orphan designations (2001-2010), a specific treatment is still not available for most rare diseases. As a consequence, patients with rare diseases are not only disadvantaged in terms of likeliness and timeliness of being accurately diagnosed, on top of that they experience unequal access to therapy in comparison with patients suffering from ‘common’ diseases. In the past decades, this unfair situation gained recognition as a serious public health problem requiring a special encouragement for the development of orphan drugs.[3]

2.1.3.2 Rare cancers

For many rare cancers the same broad categories of common cancer therapies are offered: e.g. surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, hormonal therapy and angiogenesis inhibitors. The choice of treatment depends mainly on how advanced the disease is. Additional treatments may be indicated when a tumour provokes specific symptoms (e.g. corticosteroids to reduce pressure within the skull, medicines to prevent seizures in patients with glioma).

In some situations, complex treatments may be indicated. Examples are cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in case of peritoneal surface tumours or stem cell transplantation for hematologic and autoimmune cancers.

Radiotherapy is more and more complex and implies a larger range of treatments (e.g. proton therapy for tumours located in the brain, at the base of the skull or in the eye; gamma knife radiosurgery to treat difficult tumours in the head and neck area, malignant gliomas, pituitary tumours and meningiomas; stereotactic body radiation therapy used to treat small, early-stage tumours of the lung, or isolated recurrences or metastases from various cancer types).

New targeting therapies are in development for patients with specific gene mutations. An increasing number of institutions are conducting genetic and genomic analyses on tumour specimens.

When focusing on rare cancers, several therapeutic challenges can be listed. As is the case for rare diseases too, the interest from the pharmaceutical and biotechnology industry in rare cancers is minimal. Research and development in the area of rare and lethal cancers is not prioritised because of the “small market share”. Fortunately, it's plausible that new, targeted drugs that work in more common cancers might also have a benefit in rarer cancers. In addition, orphan drugs are developed to

help patients in specific rare situations, advanced disease stage, or after failure of other therapeutic strategies (e.g. 1,2:5,6-Dianhydrogalactitol for the treatment of glioma, Temsirolimus for the first-line treatment of advanced renal cell carcinoma that meet at least three of six prognostic risk factors, Trabectedin for the treatment of advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide).[12]

Despite the large toolbox of useful treatments, the small number of patients with rare cancers hampers the execution of meaningful clinical trials that can identify the most effective treatments or the best treatment sequence in a reasonable timescale. Without clinical trials, it is extremely delicate to compose standard treatment protocols. This also involves that it is fairly impossible for non-experienced doctors to know which approach is most adequate in a given situation.

2.2 The organisation of care for patients with rare diseases

At a Belgian level, the Chamber of Representatives approved a resolution on an '**Action plan for rare diseases and orphan drugs**' in February 2009. Within the framework of the Programme 'Priority to chronic care patients!', the Fund for Rare Diseases and Orphan Drugs, managed by the King Baudouin Foundation, has been financially supported for two years (2009-2011) to develop a **proposal** for a Belgian Plan for Rare Diseases.[6] In addition, financial support was provided in 2010 and 2011 for the umbrella patients' association "Rare Diseases Organisation Belgium" (RaDiOrg, http://www.radiorg.be/homepage). The target population of the Belgian Plan should be all individuals, of either sex, at any moment in their life, affected by a rare disease, and who experience a specific need which is not sufficiently covered by the current medical, paramedical and/or social care system. In this proposal, rare diseases were defined as those life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. A low prevalence was defined as a prevalence of less than 5 per 10 000 in the community.[6]

Patient representatives, physicians, paramedical staff, insurance organisms, social service representatives, members of industry, the Orphanet Belgium team and the administration participated in 8 working groups and developed a set of 42 recommendations grouping specific measures within 11 action domains (i.e. improving the quality of diagnosis, therapy and patient management by setting up expert centres and expert networks; codifying and inventorying rare diseases; information and communication; patient empowerment; training and education of health professionals; improving access to and financing of diagnosis; improving access to and financing of treatment; comprehensive care for the patient; promoting research and transfer of research to diagnostics and treatment; management of the future Belgian Plan for Rare Diseases; ethics and governance).

Eight Belgian Centres for Human Genetics already play an important role in the diagnosis of rare diseases and provide a state-of-the-art genetic consultation.[6] In addition, 21 multidisciplinary **reference centres for specific rare diseases** or groups of rare diseases have been installed: 6 centres for neuromuscular disorders, 7 centres for cystic fibrosis, and 8 centres for hereditary metabolic diseases. Apart from these centres, expertise on many other specific rare diseases is available in many teaching and peripheral hospitals.[6]

The Fund for Rare Diseases and Orphan Drugs proposed three structures to combine national expertise while encouraging networking at a European level: Centres of Expertise (CE), Centres for Human Genetics (CHG), and a Liaison network for Rare Diseases (LRD). More details can be found in chapter 7.2.1.

2.3 The organisation of care for patients with rare cancers: the patient's perspective

On average, patients with rare cancers are younger than patients with common cancers.[4] This finding is compatible with the recognition that compared to more common cancers, rare cancers more often have a large genetic component to their aetiology.[14] Essentially all childhood cancers and most cancers (e.g. sarcomas and lymphomas) in persons up to 39 years are rare.[4] From the age of 40 years on, the more common cancers, such as breast, prostate, colon, rectum and lung, became increasingly prominent.[4]

Rare cancers are a **challenge to clinical practice**: diagnostic, staging and treatment experience are often limited, even in major cancer centres.[15] Because of the paucity of expertise, rare cancers are frequently **diagnosed late or misdiagnosed**, resulting in additional suffering for the patients.[16] Once the correct diagnosis is made, patients and physicians may struggle to find the information they need about the disease, how it will affect the patient and what the best treatment options are. Some cancers may require a **complex treatment** (for example very complex surgery for patients operated for pancreatic cancer) and/or a highly multidisciplinary approach, or are so specific that they require treatment with orphan drugs.[6, 17] Because specialists are few or equipment extremely expensive (e.g. Hadron therapy), treatment may require travelling very long distances, possibly even abroad. For many rare cancers, there are no evidence-based clinical guidelines available.[18] New treatments are difficult to evaluate since too few patients are available for adequately powered trials. For many rare cancers research is limited to case reports or small retrospective series, for which substantial selection bias cannot be excluded. Yet, significant advances in the treatment of some rare cancers (e.g. malignancies that arise in childhood, gastrointestinal stromal cancers, anal cancer) have been made as a result of national and international collaborative trials.[19]

In Belgium, patients with a rare cancer can be treated in any hospital registered with a care programme for basic oncology care and/or an oncology care programme. No hospital has been officially appointed as reference centre for specific rare cancers. As a consequence, patients diagnosed with a rare cancer do not know where they have to go to be offered optimal care. Due to the rarity of their condition, health professionals often have limited or no experience in diagnosing, supporting and treating them. Even if appropriate services exist, lack of communication, coordination and acquaintance makes these services often hard to access for patients and their relatives. Therefore interesting initiatives have been taken by some European member states to coordinate services for these patients. They are described in Chapter 6. A few of them have adopted a differentiated model where adults with rare cancers are referred to **reference centres** (also called centres of excellence). These centres have to meet a set of criteria that not only focus on procedural volume, but also on the available infrastructure, specialization of medical professionals, and outcome measures which have to be reported on a regular basis.[20] Healthcare facilities that provide a full range of cancer care services for adults, delivered by multidisciplinary teams with subspecialty training and distinguished clinical expertise in treating complex and rare subtypes of cancer are officially recognized.[21]

The goals are universal: to raise the quality of care delivered to patients with rare and complex cancers and to help them find specialty care at facilities proven to have delivered better overall outcomes.

3 THE BURDEN OF RARE CANCERS IN BELGIUM

3.1 Introduction

The purpose of this chapter is to document the incidence and the 5-year relative survival of all cancers diagnosed in Belgium, based on several years of registration by the Belgian Cancer Registry (BCR). Specifically, we aim to estimate the burden of rare cancers in Belgium by using the RARECARE threshold for the identification of rare cancers and the RARECARE typology for their classification.

3.2 The threshold of rarity and the typology of rare cancers

As of today, there is no internationally agreed definition of rare cancers. In Europe, the definition elaborated by the RARECARE network, based on an incidence threshold of 6 cases/100 000 inhabitants, has been endorsed by several cancer organisations, among which the Belgian Cancer Registry, and will be used in this report.

The value of this threshold is of course somewhat arbitrary and other thresholds are being used abroad. For example, in the USA, rare cancers are defined based on a threshold of 15 cases/100 000 inhabitants.[14] In the RARECARE project, experts opted not to use a lower threshold (e.g. <3/100 000) in order not to exclude some cancers like glial tumours, epithelial cancers of the oral cavity, soft tissue sarcomas, because these cancers are often inadequately diagnosed and treated (in relation both to lack of knowledge and lack of clinical expertise) and clinical research is seldom performed.[4] In addition, it should be mentioned that some common cancers have specific subtypes that are uncommon and hence require a different treatment approach than the common cancers. These subtypes are not within the scope of this report, and are not identified in the RARECARE classification either.

In the RARECARE typology, the definition of each tumour entity is based on a combination of morphology and topography codes[a]. The list encompasses 3 hierarchical layers: bottom, middle and top layers. The details on the typology of the RARECARE list are given in Appendix 1. The bottom layer corresponds to the WHO names of the individual cancers with their corresponding ICD-O-3 codes. These bottom layers are grouped into middle layers that are considered to require similar clinical management and research. The middle layers are further grouped to top layers that are considered to involve the same clinical expertise and patient referral structure and form therefore the most appropriate basis of discussion for the organisation of rare cancer care.[4] In this section, we focus on the top layer (layer 1).

To facilitate the reading, the layers 1 were grouped into large families corresponding roughly to main anatomic locations (head and neck, thorax...), to main body systems (digestive system, genital system, ...) or to main types of cancers (sarcomas) (see Table 1 and Table 2).

3.3 Data sources and methods

All calculations mentioned below have been performed by the Belgian Cancer Registry.

3.3.1 Incidence

All new cancers, invasive or not, diagnosed in adults (15+) and reported to the Belgian Cancer Registry between 2004 and 2010 (7-year period) are included. There is one exception: the basal cell carcinoma of the skin, typically not reported in national cancer statistics as it rarely metastasises or kills. Incidence is computed on the adult population (15+) for the same period. The RARECARE typology (layer 1 and layer 2) is used to classify all these tumours. The integral table reporting the number of new diagnoses by incidence year for Belgium during the period 2004-2010 (both sexes) can be found in Appendix 1.

---

[a] The topography code indicates the site of origin of a neoplasm; in other words, where the tumour arose. The morphology code refers to the cell type that has become neoplastic and its biologic activity; in other words, it records the kind of tumour that has developed and how it behaves. (source: US National Cancer Institute).

3.3.2 Relative Survival

Relative survival is used as a measure of cancer survival, excluding the effect arising from different background mortalities. This is calculated as the ratio of the observed survival in a group of patients to the expected survival in a comparable group of individuals from the general population; the latter can be derived from life tables for an individual country. For the current report, expected survival calculations were based on sex-, -age, -region and calendar-year-specific Belgian life tables.[22, 23]

3.3.3 Grouping of cancers

The top layers of the RARECARE list have been used to classify tumours (see Table 1). During the preparatory phase of these analyses, minor inconsistencies were discovered on the RARECARE list published on their website (http://www.rarecare.eu/rarecancers/rarecancers.asp). Experts from the RARECARE group were contacted and suggested modifications, which were applied to categorise the cancers. As a consequence, the classification of tumours used for this project deviates slightly from the "official" RARECARE list.

3.4 The burden of rare cancers in Belgium: results

3.4.1 Incidence and number of patients with rare cancer

On average, almost 62 000 new tumours are diagnosed in the adult population each year in Belgium. Of those, 4 100, i.e. 7%, are considered rare tumours (i.e. with an incidence < 6/100 000). About 25% of rare tumours affect the digestive system (mainly liver and gallbladder) and 23% are haematological malignancies. The other 50% is spread over different families (e.g. female genital system, male genital system, head and neck) (Table 1 and Figure 1). Such distribution corresponds roughly to the epidemiology of rare cancers at the European level,[4] with the exception of neuroendocrine tumours (NET). In Belgium, neuroendocrine tumours present a yearly incidence of 7.3/100 000/year and as a consequence do not fit with the RARECARE definition of rare cancers. This higher incidence was caused by the different coding of 'Carcinoïd tumours of the appendix'. The European network RARECARE coded them previously as benign ("behaviour 1"), whereas the Belgian Cancer Registry followed for this report more recent international guidelines and coded them as invasive ("behaviour 3"), which thus increases the reported incidence above the threshold. The family of neuroendocrine tumours is thus not considered as rare.

Detailed incidence data distributed by layers 1 within each family are presented inTable 1. Layers 1 are sorted by decreasing order of frequency. Frequent tumours are highlighted in green. Rare tumours are highlighted in orange (yearly incidence between 3 and 6/100 000 adults) and very rare tumours in yellow (yearly incidence less than 3/100 000).

Table 1 – Classification of groups of tumours (layer 1 in RARECARE), by family and by decreasing incidence within the family (yearly absolute number of new cases, incidence in Belgium in the adult population, 2004-2010 and 5-year relative survival)

Family	Label	N /year	Incidence 15+ N/ 100 000/year	5-year Relative Survival (%)
Head and neck	Epithelial tumours of hypopharynx and larynx	894	10.17	53.3
	Epithelial tumours of oral cavity and lip	665	7.56	53.2
	Epithelial tumours of oropharynx	555	6.31	44.0
	Epithelial tumours of major salivary glands and salivary gland type tumours	188	2.13	68.0
	Epithelial tumours of nasal cavity and sinuses	53	0.60	54.0
	Epithelial tumours of nasopharynx	50	0.57	62.8
	Epithelial tumours of eye and adnexa	4	0.04	-
	Epithelial tumours of middle ear	3	0.03	-
Thoracic	Epithelial tumours of breast (both sexes)	9 639	109.60	88.3
	Epithelial tumours of lung	7 287	82.86	15.9
	Malignant mesothelioma	248	2.82	5.5
	Epithelial tumours of thymus	29	0.33	70.4
	Epithelial tumours of trachea	13	0.14	15.4
Digestive system	Epithelial tumours of colon	5 531	62.89	63.8
	Epithelial tumours of rectum	2 253	25.62	64.7
	Epithelial tumours of stomach	1 262	14.34	28.0
	Epithelial tumours of pancreas	1 156	13.14	6.7
	Epithelial tumours of oesophagus	889	10.11	22.7
	Epithelial tumours of liver and intrahepatic bile tract (IBT)	523	5.95	20.3
	Epithelial tumours of gallbladder and extrahepatic biliary tract (EBT)	344	3.91	19.1
	Epithelial tumours of anal canal	125	1.42	68.5
	Epithelial tumours of small intestine	87	0.99	33.9

Family	Label	N /year	Incidence 15+ N/ 100 000/year	5-year Relative Survival (%)
Female genital system	Epithelial tumours of corpus uteri	1 303	14.82	82.4
	Epithelial tumours of ovary and fallopian tube	867	9.86	43.6
	Epithelial tumours of cervix uteri	630	7.16	69.9
	Epithelial tumours of vulva and vagina	224	2.55	58.7
	Mixed epithelial and mesenchymal tumours of uterus	68	0.78	42.2
	Non epithelial tumours of ovary	37	0.42	58.2
	Trophoblastic tumours of placenta	3	0.04	-
Male genital system	Epithelial tumours of prostate	9 127	103.77	95.9
	Tumours of testis and paratestis	291	3.31	96.5
	Epithelial tumours of penis	73	0.83	67.2
Urogenital system	Epithelial tumours of bladder	2 098	23.86	55.2
	Epithelial tumours of kidney	1 406	15.98	72.6
	Epithelial tumours of pelvis, ureter and urethra	346	3.93	45.2
Haematological system	Lymphoid diseases	3 713	42.21	69.7
	Myelodysplastic syndrome and myelodysplastic/myeloproliferative disease	593	6.74	46.6
	Myeloproliferative neoplasms	509	5.79	83.9
	Acute myeloid leukaemia and related precursor neoplasms	434	4.93	27.0
	Histiocytic and dendritic cell neoplasms	9	0.10	63.1
Central Nervous System (CNS)	Glial tumours of CNS	694	7.89	22.4
	Malignant meningiomas	15	0.17	68.1
	Non-glial tumours of CNS and pineal gland	11	0.13	53.8
	Non-glial tumours of cranial and peripheral nerves, autonomic nervous system and paraganglia	8	0.09	57.9
	Glial tumours of cranial and peripheral nerves, autonomic nervous system and paraganglia	1	0.01	-
NET	Carcinoma of endocrine organs	731	8.32	92.9
	Neuroendocrine tumours	643	7.31	63.7

Family	Label	N /year	Incidence 15+ N/ 100 000/year	5-year Relative Survival (%)
Sarcoma	Soft tissue sarcoma	642	7.30	63.1
	Bone sarcoma	104	1.19	69.4
	Gastrointestinal stromal sarcoma	104	1.18	88.8
	Kaposi's sarcoma	38	0.43	78.6
Skin and non cutaneous melanoma	Epithelial tumours of skin	3 280	37.30	-
	Malignant skin melanoma	1 726	19.62	89.8
	Adnexal carcinoma of skin	73	0.83	-
	Malignant melanoma of uvea	57	0.65	65.5
	Malignant melanoma of mucosa	37	0.42	34.7

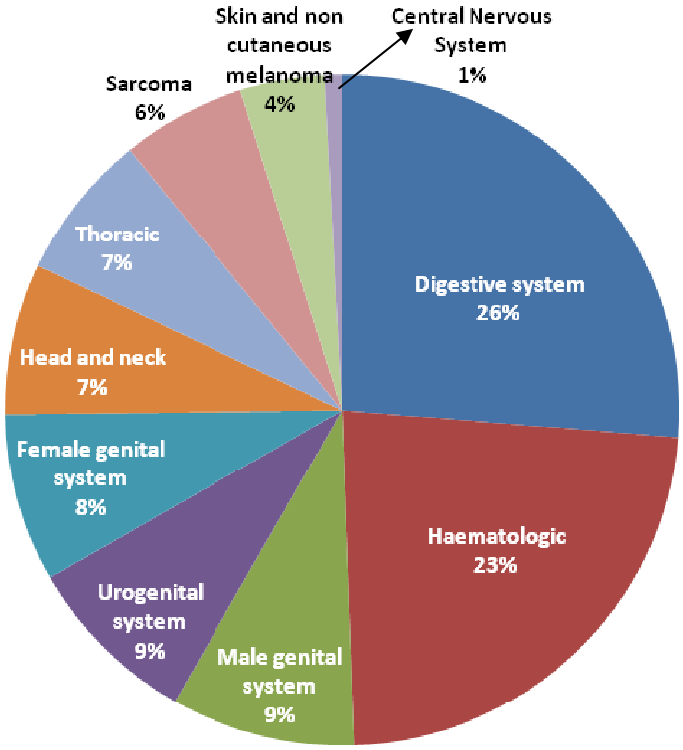
Source. Belgian Cancer Registry, data 2004-2010
Colour code: green= above 6/100 000 threshold, orange = between 3-6/100 000 threshold, yellow = below 3/100 000 threshold; "-" indicates that the relative survival could not be calculated because of the small sample size
Note. The complete RARECARE list is composed of 58 layers 1, including 'embryonal neoplasms' and 'extragonadal germ cell tumours' that are paediatric solid cancers and hence not adopted in Table 1.

Table 2 – Repartition of rare cancers in Belgium according to families identified by RARECARE

Family	Total number of new cancers/year	Total number of new rare cancers/year	Proportion of new rare cancers/total number of new rare cancers (%)	Proportion of rare cancers within a family (%)
Digestive system	12 169	1 079	26.3	8.9
Haematological cancers	5 257	951	23.2	18.1
Male genital system	9 491	364	8.9	3.8
Urogenital system	3 850	346	8.4	9.0
Female genital system	3 133	333	8.1	10.6
Head and neck	2 412	298	7.2	12.3
Thoracic	17 216	289	7.0	1.7
Sarcoma	888	246	6.0	27.7
Skin and non cutaneous melanoma	5 173	167	4.1	3.2
Central Nervous System	729	35	0.8	4.7
Neuroendocrine/endocrine tumours	1 374	0	0.0	0.0
TOTAL	**61 692**	**4 107**	**100.0**	**6.7**

Source. Belgian Cancer Registry, data 2004-2010

Figure 1 – Repartition of rare cancers by family (2004-2010)



Source. Belgian Cancer Registry, data 2004-2010

3.4.2 Relative survival

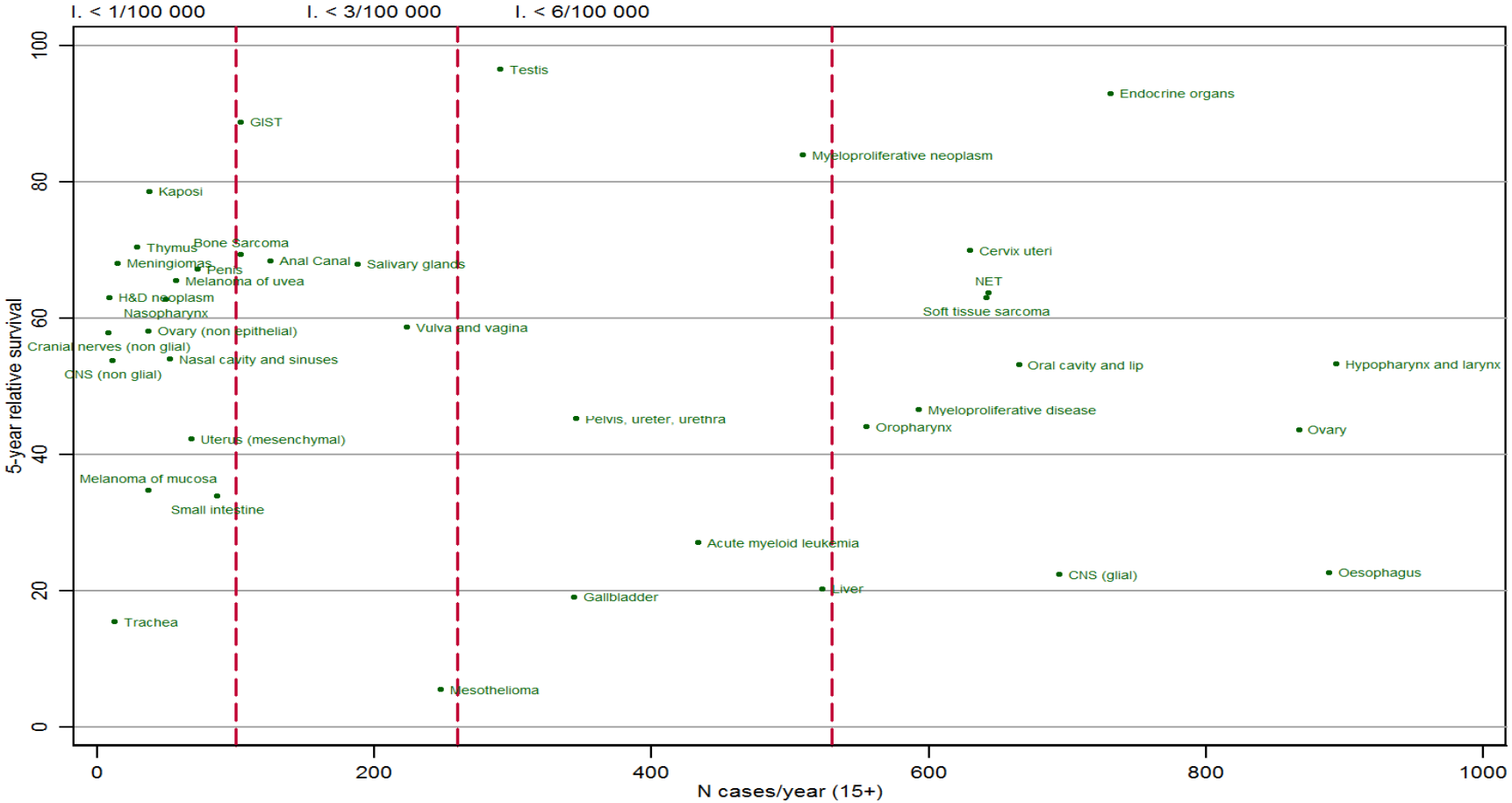
Relative survival versus annual incidence (expressed as N cases per year) is mapped in Figure 2 (for tumours with an incidence below 1 000 new cases per year) and Figure 3 (for tumours with an incidence above 1 000 new cases per year).

In Belgium, groups of rare cancers with the poorest 5-year relative survival (around or below 20%) include cancers of the trachea, the gallbladder, the liver and mesothelioma. Beyond the RARECARE threshold but limited to a maximum of 1 000 adults diagnosed per year, the following tumours are also characterised by a poor prognosis: glial tumours of the central nervous system, cancers of the oesophagus and cancers of the pancreas. Lung cancer, belongs to the group of the commonest cancers (7 000 new cases per year) and also faces a poor prognosis (below 20%).

Rarity is not systematically a precursor of bad prognosis. Gastrointestinal stromal tumours (GISTs), Kaposi's sarcomas, cancer of the testis and myeloproliferative neoplasms reach a 5-year relative survival around or above 80%.

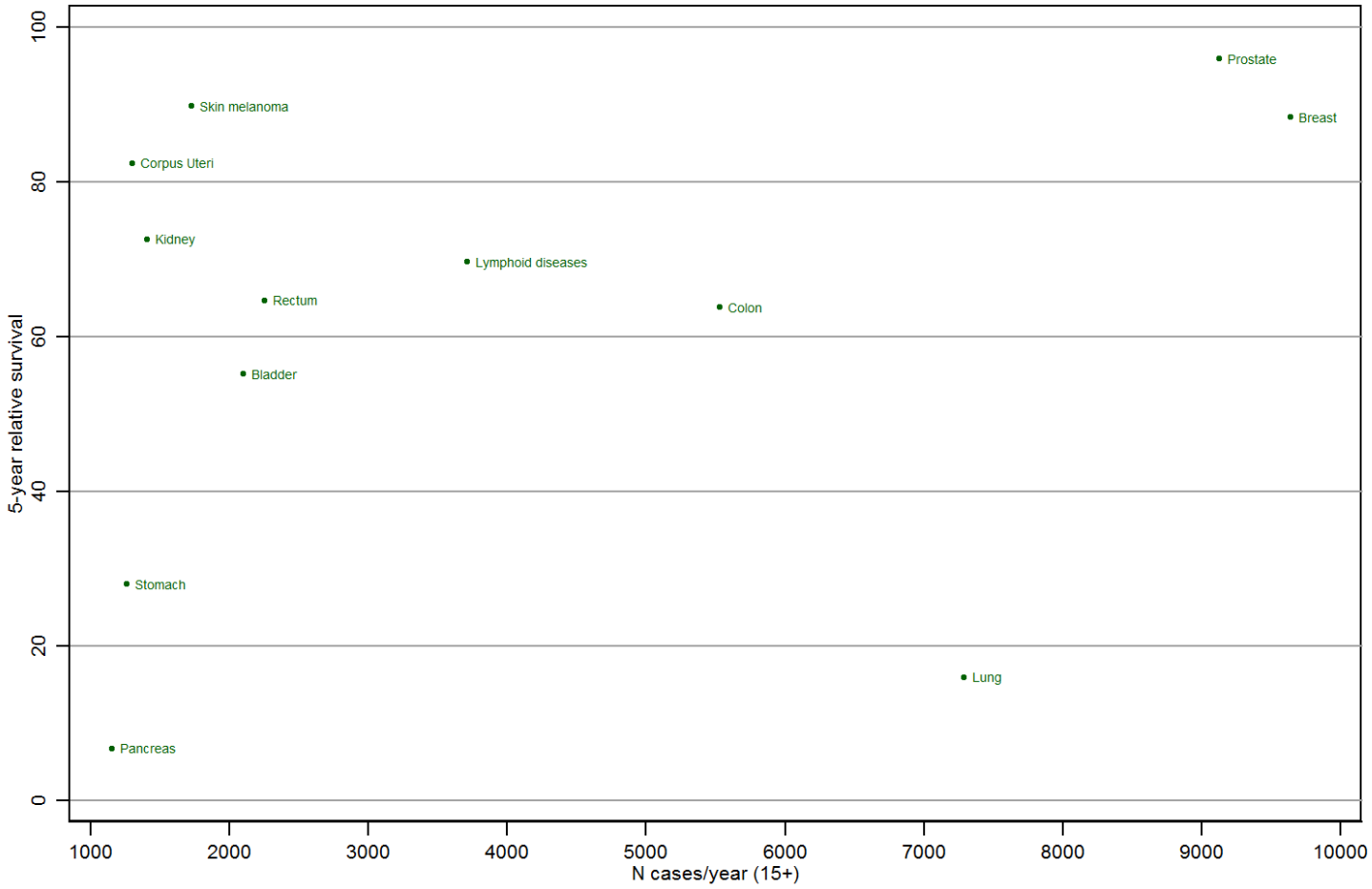
While we intended to benchmark Belgian data with the mean European results published in the RARECARE study,[4] major methodological weaknesses hampered the execution of this idea. First of all, the incidence data of the RARECARE project were 15 years old on average, covering the years 1995-2002, hence without any overlap with the Belgian data (2004-2010). As the comparison of the EUROCARE-3 data (1990-1994) and the EUROCARE-4 data (1995-1999)[24] clearly showed improvement in relative survival over the years, any difference observed in survival could be due to differences in incidence periods (different diagnostic and staging approaches, differences in therapeutic strategies). Second, large differences exist in terms of cancer outcomes across Europe, whatever the incidence periods under study, with Northern and Western countries exhibiting the best results, and Eastern countries the worst.[24] Any comparison with a “European average” that includes outcomes from Eastern countries, would lead to the spurious conclusion of superior results reached in Belgium. A sensitivity comparative analysis with a more restrictive group of European countries, for instance those of the EU-15, would be more meaningful but such data are unavailable for the moment.

Figure 2 – Yearly incidence and 5–year relative survival for tumours grouped by layer 1 (< 1 000 new cases per year) - Belgium (2004-2010)



Notes: the dashed red lines correspond respectively to incidences of 1/100 000, 3/100 000 and 6/100 000 adults. I: Incidence; CNS: Central nervous system; NET: Neuroendocrine tumours; GIST: Gastrointestinal stromal sarcoma; H&D neoplasm: Hystiocytic and dendritic neosplasm; Tumours of eye, middle ear, glial tumours of cranial nerves and carcinomas of skin are not indicated on the graph because the number of available observations was too small to calculate relative survival.
Data source: Belgian Cancer Registry, data 2004-2010.

Figure 3 – Yearly incidence and 5–year relative survival for tumours grouped by layer 1 (> 1 000 new cases per year) - Belgium (2004-2010)



Source. Belgian Cancer Registry, data 2004-2010

3.5 Discussion

Recently, the European initiative RARECARE has shed the light on the burden of rare cancers in Europe (www.rarecare.eu), by providing for the first time accurate data on the number of patients diagnosed with a rare cancer, and on their survival after diagnosis. The merit of collecting data from more than 70 European cancer registries, and setting up for the first time a hierarchical classification of rare tumours certainly deserves acknowledgement. Meanwhile, since the RARECARE data are at the best 10 years old, and since regional variability exists in cancer incidences across Europe, the RARECARE data were insufficient and hence rendered a meticulous analysis of Belgian data imperative.

The present analysis results from a close collaboration between different partners. The Belgian Cancer Registry analysed the exhaustive Belgian cancer database over a 7-year period and applied the RARECARE classification on those data. The European RARECARE group provided useful feedback to resolve inconsistencies in some classifications levels. Finally, KCE experts analysed these data and synthesised the information in this chapter.

Although the label 'rare' would presume that only few persons are affected by rare cancers, the **number of adults** being diagnosed with a rare cancer is **estimated at 4 000 a year in Belgium**. They represent 7% of all adults being diagnosed with a cancer. The two most common families of rare cancers are digestive cancers (mainly tumours of the liver and gallbladder) and haematological malignancies (mainly myeloproliferative neoplasms and acute myeloid leukaemia). However, for a majority of rare cancers, **less than 100 patients** a year are being diagnosed **with a specific rare cancer** in Belgium. This fact is of utmost importance when planning a better organisation of care for those patients.

Quantitative data on the incidence of rare cancers form certainly an important starting point when considering an improved organisation of care for patients with rare cancers in Belgium. However, it is also wise to recognise some limitations. First, like with all thresholds, the artificial limit of 6 new cases/100 000 adults per year has the unpleasant consequence that similar types of cancers with close incidences lying just below or just above the threshold are considered rare or not. Both from a clinical point of view as for an organisational approach, such distinction is meaningless. For example, myelodysplastic syndrome and myelodysplastic/ myeloproliferative diseases on the one hand, and myeloproliferative neoplasms on the other hand, have respective yearly incidences of 6.7/100 000 and 5.8/100 000, while only the latter is labelled rare. Second, some cancers require a high level of surgical expertise, and a call for a critical caseload to maintain sufficient expertise. Oesophageal or pancreatic cancers are typical examples. Both cancers are not so infrequent (around 1 000 cases per year), while less than half of those patients will undergo a surgery, rendering oesophagectomy and pancreatectomy rare surgical interventions in addition to being complex interventions. This speaks in favour of taking also the criteria of complexity of the cancer management into account, and not only the raw incidence numbers. Third, some rare forms of more frequent cancers are not labelled rare because the threshold is applied to layer 1 and not to layer 2 of the classification (for instance, endocrine tumours of the lung are counted within the “tumour of the lung” group, and hence are not considered rare, whereas they are actually rare).

4 ORGANISATION OF CARE IN ONCOLOGY IN BELGIUM

4.1 The Belgian Cancer Plan

In 2007, a panel of 11 Belgian oncologists published a white book on the status of several aspects of cancer care in Belgium.[25] These authors formulated innovative recommendations for improvement and anticipation of new challenges, such as the effect of ageing on cancer incidence. This White book already recommended to develop and to re-analyse the repartition of the care programmes in oncology but also to put in place dedicated programmes for **rare cancers** and **paediatric cancers**.

The Minister for Public Health and Social Affairs, Ms. Laurette Onkelinx, launched after consultation of the field in March 2008 a first comprehensive National Cancer Plan 2008-2010[1] that effectively addressed many of the issues raised in the 2007 analysis of cancer care in Belgium.

The primary objectives of this Plan are to reduce cancer-related mortality and morbidity and to improve quality of life of cancer patients and their families, through psychological support. The plan focuses on three main topics:

- **Prevention** (e.g. smoking cessation, life style, nutrition, occupational exposure, HPV and hepatitis vaccination, information about the risks of sun exposure on the development of melanoma) and **screening** (e.g. screening programmes for breast, cervical and colorectal cancers, specific attention to familial and genetic cancers (e.g. the breast screening by mammography and ultrasound is free of charge), reimbursement of additional exams performed in women with positive screening results);
- **Treatment** (e.g. multidisciplinary oncological consult (COM/MOC), increase of COM/MOC honorarium, support and access to innovation, recurrent evaluation of existing treatments, access to high impact treatments, flexible reimbursement system for newly developed drugs as well as removal of ineffective ones, increasing hospital financing to enlarge their specialized staff in the oncology care programmes, improved reimbursement for a number of cytotoxic agents, involvement of general practitioners) **and support** (e.g. increase in number of trained psychologists, improvement of palliative and supportive care, financial support for diagnosis announcement consultation, financial support to patients and increasing effort in revalidation and reintegration, attention to patients' rights, initiatives to improve oncological care for older patients in collaboration with programmes for geriatric care);
- **Research and innovative technologies** (e.g. structural and project-linked financing of academic research, creation of a tumour bank, creation of a National Cancer Institute and networks, evaluation of the feasibility of a hadron therapy centre in Belgium, support for translational research).

Thirty-two measures were translated into 62 actions. These actions are implemented by the Federal Service of Public Health and the National Institute for Health and Disability Insurance (INAMI/RIZIV). The Belgian Cancer Plan was prolonged and additional measures were progressively adopted.[26] Action 13 specifically relates to the care and treatment of patients with rare cancers, aiming to define qualitative and quantitative criteria for their treatment.

4.2 The Belgian Cancer Registry (BCR)

The first goal of the Belgian Cancer Registry (BCR) was to create a population based cancer database in order to describe the incidence, survival and prevalence in Belgium for all types of cancers, irrespective of whether it is a frequent or a rare cancer. A cancer registry indeed should be a basic tool to serve public health by monitoring changes in cancer occurrence and prognosis.[27]

The foundation in 2005 of the new BCR by all Belgian authorities involved in public health and new legislation initiatives since 2003, forced a breakthrough in cancer registration. The Royal Decree of the oncological care programmes in 2003[b], the reimbursement of the multidisciplinary oncological consultation (COM/MOC) and the specific law on the Cancer Registry in 2006[c] provided a firm legal basis for cancer registration in Belgium. This legislation makes cancer registration compulsory for the oncological care programmes and for the laboratories of pathological anatomy and clinical biology (haematological malignancies).

Hospitals are obliged to register all new cancer diagnoses, irrespective of whether a cancer case is discussed during a COM/MOC and irrespective of whether it is a rare cancer. Each tumour has to be recorded by means of a standard form including a confined set of variables. This data set uses the International Classification of Diseases for Oncology (ICD-O)[28] to code the tumour characteristics (primary tumour localization and histological diagnosis). The RARECARE classification is also based on these two axes in order to be able to define the different layers of the Rare Cancer classification system.[4] The stage of the cancer always has to be recorded according to the most recent TNM Classification of Malignant Tumours.[29]

Laboratories of pathological anatomy encode the received specimens following classification systems and rules approved by the Consilium Pathologicum Belgicum. Every malignant diagnosis is encoded and annually transferred to the Belgian Cancer Registry, accompanied by the written protocols. Thanks to an extended collaboration with the pathologists, a registration of all cyto-histological specimens taken for early diagnosis and screening for breast, colorectal and cervical cancer is ongoing. As a result, not only common cancers but also the rare cancers in these groups are detected and registered.

The law authorises the use of the national number of social security (NNSS) as the unique identifier of the patient. The use of this unique number favours linkage with other available medical and administrative data. Furthermore, through linkage with the Crossroads Bank for Social Security, the NNSS enables the Cancer Registry to perform active follow-up on the vital status of the patients. Such a linkage not only requires the authorization of the Sectoral Committees of the Privacy Commission but also implies severe measures and rules for privacy protection and confidentiality.

Data on cancer incidence are publicly available for Belgium from 2004 on and for the Flemish Region from 1999 onwards. The most recent incidence data in October 2013 are from the year 2011. A detailed overview of cancer incidence and survival results in Belgium, the Walloon Region, the Brussels-Capital Region and in the Flemish Region have been published in specific booklets.[23, 30] Both publications mostly consider and describe the more frequent cancers. Rare cancers, defined as a group of malignancies with an incidence rate equal to or lower than 6/100 000 person years,[4] are relatively low burden at the population level and therefore often not prioritised for publication by e.g. the Cancer Registry and the Public Health authorities.

Cancer incidence, prevalence and survival data are traditionally published and communicated by ICD-10 codes which represents a rather low granularity for tumour specifications. Nevertheless, the use of the ICD-O and TNM classifications at the Cancer Registry allows to report more specifically and on much more detail. They are certainly available at the

---

[b] Koninklijk Besluit houdende vaststelling van de normen waaraan het zorgprogramma voor oncologische basiszorg en het zorgprogramma voor oncologie moeten voldoen om te worden erkend. Belgisch Staatsblad, 21 maart 2003. Arrêté Royal fixant les normes auxquelles les programmes de soins de base en oncologie et les programmes de soins en oncologie doivent répondre pour être agréés. Moniteur Belge, 21 mars 2003.

[c] Wet houdende diverse bepalingen betreffende gezondheid van 13 december 2006, artikel 39. Belgisch Staatsblad, 22 december 2006. Loi portant des dispositions diverses en matière de santé du 13 décembre 2006, article 39. Moniteur Belge, 22 décembre 2006.

Cancer Registry at specific request. An example can be found in the publication 'Cancer Incidence in Belgium, 2010. Special Issue on Cancer in Children and Adolescents'.[31]

A second mission of the BCR with regard to rare cancers is the participation in studies on the evaluation of quality of care in oncology. A Cancer Registry should be a basic tool to serve oncology by studying access and variation in quality of care and outcomes, including the patient perspective, and cause-specific mortality. The methods of quality of care research also include interpretation of context and regular feedback to the clinicians involved. This is not only for frequent cancers, also rare cancers are included in this mission. The Cancer Registry actually participates in two different pathways.

The linkage of cancer registration data with data on reimbursed diagnostic and therapeutic acts (nomenclature and pharmaceutical products) of the health insurance allows the calculation of process and outcome indicators in order to evaluate the quality of care in oncology. An example of this methodology and results can be found in the specific KCE reports on testicular cancer[32] and oesophageal cancer.[33] Moreover, in the context of a specific project on rare cancer, financially supported by the 'Vlaamse Liga tegen Kanker', the Belgian Cancer Registry performed a descriptive analysis of rare cancers in Belgium and the Flemish Region.[59] Their rarity ensures that small numbers for very different malignant diseases have to be taken into account and this hampers statistical analyses. Incidence, trends in incidence and survival are presented by organ system in the report. Variability in treatment, volume of treatment per centre and outcome results are only presented for a selected group of cancers (e.g. oropharynx cancer, mesothelioma, vulvar and vaginal cancer).

Another possibility to study the quality of care is within the context of a prospective registration project, such as the well-known project Procare. This methodology allows the implementation of a clinically relevant data set in order to calculate well-defined process and outcome indicators.

Both methods mentioned above have their advantages and disadvantages; these were already discussed in previous KCE reports.[34] It is a challenge for the Cancer Registry and for all stakeholders to make use of available administrative databases and to carefully select prospective registration subjects in the context of rare cancers.

A third mission of the BCR in the context of rare cancers is the management of the Belgian Virtual Tumour bank or the Biobank Catalogue (accessed on http://virtualtumourbank.kankerregister.be/tumourbank.aspx?lang=TB_EN, October 29th 2013). This online catalogue of available tissues provides many opportunities for scientific research, not only for frequent cancers, but especially for rare cancers, considering the sometimes scarce availability of such tissue for research.

4.3 Laboratories for pathology

4.3.1 Introduction

Pathology is a medical specialty that involves the study of the morphological modification of organs in the course of pathological processes. It is based on the analysis of the cells and tissues of the organism, however obtained, to provide diagnostic and prognostic information in the form of an integrated pathology report. Pathology also provides a means of assessing the outcome of treatments. Other terms are frequently used with similar focus (histopathology, surgical pathology, anatomic pathology or cellular pathology including cytopathology).

4.3.2 Licensing and accreditation of laboratories

Licensing of laboratories for Pathology is mandatory (since 1st March 2013) in Belgium in order to obtain the reimbursement of routine pathology tests as specified in the Belgian nomenclature Art. 11 and Art. 32 (RD on the recognition of pathology laboratories, 5th December 2011).

ISO 15189 Accreditation is mandatory to obtain the reimbursement of **specific procedures** – mainly molecular biology tests – as described in Art 33bis and Art 32 of Belgian nomenclature.[35]

On 1st September 2013, 104 pathology laboratories were licensed, 22 of them were ISO15189 accredited for at least one test (source: ISP/WIV).

Table 3 – Main differences between licensing and accreditation activities

Characteristics	Licensing of the laboratory	Accreditation of the laboratory
Legislative basis	RD 5/12/2011	RD 7/6/2007, RD 4/5/2009
Reimbursement of procedures (nomenclature)	Art 32, Art 33bis and Art 11	Art 33bis, Art 32 (HPV)
Scope of the evaluation	Conformity	Competence to perform specific tests
Criteria	RD 5/12/2011 and Practice Guideline	ISO 15189
Extent	The whole laboratory	Specific tests
Responsibility	FPS Public Health/Minister	FPS Economy
Evaluator	ISP/WIV / visits	BELAC / audits
Mandatory	Mandatory from 1/3/2013	Mandatory for labs molecular biology (oncology and virology) and for pathology labs performing molecular diagnostic tests

Source. Romaric Croes & Herwig van Dijck. L'AR du 5/12/2011 - Au sujet de la Commission d'Anatomie Pathologique et les implications pour nos laboratoires, 17.11.2012

4.3.2.1 Licensing procedure

Since 1st March 2013, the **Scientific Institute of Public Health (ISP/WIV)** is responsible for Quality assurance and licensing of pathology laboratories, on behalf of the Minister of Public Health. To this intent, ISP/WIV works in concert with the Commission of Pathology, as described in The Royal Decree on the Recognition of Pathology laboratories (5th December 2011).

The Commission of Pathology consists of 14 (+ 14 substitutes) pathologists supplemented with 6 government officers (representatives of ISP/WIV, INAMI/RIZIV and FPS Public Health). They define the technical fields that have to be evaluated and the frequency of these evaluations by the ISP/WIV.

The Commission advises the Minister of Public Health about the licensing of labs and of all issues related to anatomic pathology in general; it also advises the National Council for Quality Promotion, and the Technical Medical Council (INAMI/RIZIV) for issues related to the nomenclature. Different Working Groups (Practice Guidelines, External Evaluation Programmes, Legislation...) have been established since the installation of the Commission in October 2012.

Counting from the date of a definitive license, the pathology laboratories dispose of a term of 5 years to complete a Quality Manual describing their system of quality management. Pre-analytical, analytical and post-analytical procedures have to be detailed as well as the overall organization of the laboratory of pathological anatomy and the qualification of auxiliary personnel.

A national programme for external evaluation is mandatory for all licensed labs. The ISP/WIV carries out administrative evaluations complemented by on-site visits and identifies laboratories that do not meet the eligibility criteria set by the Commission of Pathology.

4.3.2.2 Accreditation procedure

Since 1st August 2006, BELAC is the only **Bel**gian **Ac**creditation Body. It was established by the provisions of the Royal Decree of 31st January 2006 and is placed under the responsibility of the FPS Economy, Small and medium-sized enterprises (S.M.E.s), Self-employed and Energy. Accreditations issued under the authority of BELAC are recognised by the Belgian State. Accreditation is issued after an audit focusing on laboratory organization and implementation of testing techniques. This audit has to establish the competence of the laboratory to perform specific tests, in compliance with the requirements of ISO15189:2007.

The accreditation form with the 'scope' for each laboratory can be found on the BELAC website (http://economie.fgov.be/belac.jsp) and specifies the code, the parameter, the type of sampling, the technical method (analyzer) and the kit used by the lab.

Oncology tests that require a formal accreditation ("Article 33bis. NIHDI nomenclature § 1. Molecular Biologic tests on human genetic material in acquired disorders") include HER-2 ISH, KRAS mutation analysis and a variety of molecular tests important in hematologic oncology.

Pharmaco-diagnostic testing on biopsy material (immunohistochemistry for estrogen/progesterone receptors, c-kit, EGFR and HER-2) does not require accreditation (but has to be performed in a licensed laboratory).

4.3.3 Organisation of second opinion in pathology

4.3.3.1 Context

Pathology is still largely considered as the '**gold standard**' tumour diagnosis. With very few exceptions, definitive therapy for cancer should not be undertaken in the absence of a tissue diagnosis. It is the pathologist's role to provide an accurate and specific diagnosis to enable the clinician to develop an optimal plan of treatment and, as far as possible, to give an estimate on the prognosis. Only a few years ago the simple diagnosis "benign" or "malignant" provided the clinician with all information necessary to provide appropriate care for the patient. This is no longer the case. Cancer is not a single disease. There are more than 300 distinct varieties of tumours, each with a characteristic biology.[36] Some of these tumours are very rare, such that pathologists may encounter them only once or twice in their entire professional career. This is why providing an accurate diagnosis in a rare cancer case can represent a real challenge for pathologists. At the same time, it is extremely important, especially in the era of personalized health care, to combine information from pathology, molecular biology and clinical practice to set up an appropriate treatment plan for these rare cancer cases.

The success of therapeutic options for cancer treatment essentially depends upon accurate diagnoses. For rare and complex cancers, correct typing, staging and grading can be challenging. Also, the assessment of important prognostic and predictive factors is prone to errors and needs strict quality control.

Rare Cancers Europe (RCE) is a multi-stakeholder initiative supported by the European Society for Medical Oncology (ESMO) dedicated to placing rare cancers high on the European agenda. Recommendation 36 reads: "we encourage the development of innovative approaches to raising general practitioners' and pathologists' awareness about rare cancers, especially the symptoms and tumour characteristics that signal the need to refer the patient for a second opinion" (see http://www.rarecancerseurope.org/About-Rare-Cancers).

Pathologists have long understood the significance of misdiagnoses and the value of **second opinions** and **panel revisions**. Second opinions on pathology diagnoses are routinely used intra-departmentally or are reviewed extra-departmentally by a panel of experts for a limited selection of cancer cases.

However, there are no criteria to identify the cases submitted for second opinion. Usually, there is no organized registration of the intra-departmental pathology review.

Determining the type of pathology where a diagnostic confirmation is mandatory is quite difficult. These conditions are related to sub specialization of Pathology associated with high diversity and complexity of lesions and an increasing number of ancillary techniques necessary in obtaining accurate cancer diagnosis. One could define a 'difficult lesion' as a lesion where the interpretation of the pathology data (including standard staining, immunohistochemistry and molecular techniques) does not allow the pathologist to have an accurate diagnosis.

There is ample and consistent proof that expert review of pathology data can result in a change of diagnosis in a significant proportion of cases (ranging from a minor disagreement over tumour grade, which may nonetheless influence treatment decisions, to a false positive - or false negative - diagnosis of malignancy).[11, 37-43] For example, twenty to 25% of sarcoma cases referred to CONCATINET, the European sarcoma network, for a second opinion had been misdiagnosed.[18] A finding that is not so surprising to the authors since on average general practitioners and pathologists are confronted with one or two cases in their career. Another study on the pitfalls in the diagnosis of neuroendocrine tumours (NET) revealed that "neither laboratory tests nor octreoscans are completely reliable diagnostic tools because other clinical disorders or atypical radiological findings may mimic a carcinoid, hence leading to an erroneous NET diagnosis."[44]

Timely expert review is therefore in the best interests of the patient, but many pathologists are faced with questions over how, when and to whom, these cases should be referred. Moreover, sending cases to outside institutions incurs a cost for both the referring and the receiving laboratory. Currently there is no funding of nor a legal basis for this practice of second opinion in pathology.

4.3.3.2 Legal aspects

To date, no legislation regarding the responsibilities of caretakers in case of 'second opinion' has been established. Before implementing a formal procedure of diagnostic confirmation in Belgium, all legal aspects (liability, privacy matters…) will have to be considered and dealt with. A firm legal base will ensure the rights of patients and physicians while encouraging good clinical practice.

4.4 Existing care programmes in oncology

4.4.1 Care programmes for basic oncological care and oncology care programmes

The Royal Decree of 21st March 2003 stipulates the **care programmes for basic oncological care**[d] and **oncology care programmes**[e]**.** Both programmes aim at reinforcing the provision of high quality care for cancer patients.

Care programmes are coherent sets of care services for a well-defined target patient group. Firstly, the programme is defined by the case treated and the type of care given. Then, norms describing infrastructure, number of personnel, minimum activity level, etc. are allocated to the care programme.

In the Royal Decree of 21st March 2003, a distinction is made between:

- **Care programmes for basic oncological care** that focus mainly on diagnosis and less complex treatment. In principle, each hospital that does not have a recognition for an oncology care programme, has to offer a care programme for basic oncological care;
- **Oncology care programmes** that have to offer more advanced diagnostic options as well as various therapeutic possibilities. The number of care programmes that can be installed at that organisational level is not limited.

[d] Programme de soins de base en oncologie / zorgprogramma voor oncologische basiszorg.

[e] Programme de soins d'oncologie / zorgprogramma voor oncologie.

The Decree also stresses the importance of certain aspects in the organisation of oncological care such as multidisciplinary care and coordination between care in the first line (including home care), the care programme for basic oncological care, the oncology care programme and a palliative setting. In order to get a recognition, a hospital must have a multidisciplinary Handbook of Oncology (quality manual) that includes guidelines with respect to diagnosis, treatment and follow-up of patients, referral agreements and the identity and tasks of all personnel involved. A second tool that must ensure multidisciplinary care is the organisation of multidisciplinary oncological consults, that should be attended by at least 4 physicians from different disciplines.

The number of programmes is not limited *per se*. All programmes that meet the required criteria, can be recognized (AR/KB 21.03.2003; MB/BS 25.04.2003). Globally, the number of hospitals in Belgium amounts 193 (including general, specialised, university, geriatric, psychiatric hospitals). In 2013, **106 hospitals were registered with a care programme for basic oncological care and/or an oncology care programme**; 87 hospital sites with programmes for basic oncological care and 84 hospital sites with an oncological care programme.[f]

4.4.1.1 Specific provisions for each care programme

Concerning content, the difference between both programmes is determined by the mutual agreements that are documented in the multidisciplinary Handbook of Oncology. The differences in norms are mainly situated in the medical framework, the required infrastructure and surrounding elements. More details about these requirements are reported in Appendix 2.

To enable hospitals to keep pace with innovations in the field of oncology and the tremendous increase in therapeutic options, care programmes are being placed under the supervision of the College of Oncology. In addition, the College of Oncology is responsible for the development, assessment, implementation and dissemination of good practice guidelines, and for development of quality indicators to assess the quality of clinical practice in oncology. However, despite the fact that the College is legally allowed to carry out field visits to evaluate implementation efforts and results, it has not taken this opportunity so far. In addition, it has to be realised that audits by peers face many drawbacks (e.g. uncertain objectivity, insufficient competences for auditing) and it has been recognised internationally that audits should be performed by independent experts in auditing. The European Observatory on Health Systems and Policies[45] concluded that despite the distinction between basic programmes for common cancers and specialised programmes for rarer cancers, it remains unclear which centres provide higher standards of care.

4.4.1.2 Future developments

The Royal Decree of 21st March 2003 further specifies that apart from these two care programmes, a number of **specialised care programmes** need to be developed that focus on patients with cancers that need a complex multidisciplinary approach and/or extremely specialised expertise and/or that are very rare. It also states that specific care programmes should be developed for children younger than 16 years old with an oncological illness that requires specific modalities from a diagnostic and/or therapeutic perspective.

4.4.2 Care programmes for children and adolescents with cancer

In Belgium, every year about 320 children (0-14 years) and 175 adolescents (15-19 years) are diagnosed with cancer.[31] Oncological care for paediatric patients (i.e. up to the age of 16 years old) is currently centralised in 7 centres, that receive extra financial means through the B4 part of the hospital budget, according to their level of activity and previous financing.

[f] As a hospital can certify separately different sites, the total number of sites with certified programs is higher than the number of hospitals.

Table 4 – Overview of financed paediatric centres for haemato-oncology in Belgium, since 2010

	Paediatric Centre and localisation
Wallonia	SUHOPL, Service Interhospitalier Universitaire d'Hématologie et d'Oncologie Pédiatriques Liégeois (CHU, CHR Citadelle and CHC Montegnée)
Brussels	Cliniques universitaires Saint-Luc
	Hôpital Universitaire des Enfants Reine Fabiola
	Universitair Ziekenhuis Brussel
Flanders	Universitair Ziekenhuis Gent
	Universitair Ziekenhuis Leuven
	ZNA Koningin Paola Kinderziekenhuis Antwerpen

Abbreviations: CHU (Centre Hospitalier Universitaire); CHR (Centre Hospitalier Régional); CHC (Centre Hospitalier Chrétien); ZNA (Ziekenhuis Netwerk Antwerpen).

The International Society of Paediatric Oncology of Europe (SIOP Europe - http://www.siop-online.org) stipulates that a Paediatric Cancer Unit (PCU) should see at least 50 new cases a year. For very specialised treatments, such as bone marrow transplantation or complex surgery or radiotherapy, further specialisation and defined referral pathways from the smaller to the larger principal treatment centres may be needed.[46]
In the NICE guidance 'Improving outcomes in children and young people with cancer', it is emphasised that age-appropriate, safe and effective services should be as locally as possible, not local services as safely as possible.[47]

In Belgium, the development and implementation of care programmes for paediatric haemato-oncology that can provide comprehensive multidisciplinary facilities and optimum standards of care are still ongoing. Propositions for recognition criteria were formulated by a taskforce of the Federal Public Health Service. A Royal Decree aiming at translating this proposition should be published soon.

The centres specialised in paediatric oncology that fulfil required criteria should then be recognised as reference centres and will benefit from an additional structural budget to reinforce the management of children with cancers.

4.4.3 Specialised care programme: the breast cancer clinics

Breast cancer is currently the most frequent cancer (9 908 new cases in 2010) and the most frequent cause of cancer-induced deaths in women in Belgium (2 300 deaths in 2008).[30] This situation is similar in other European countries. Facing large differences in breast cancer survival among the member states,[48-50] the European Parliament (EP) endorsed in 2003 a resolution on "Breast Cancer in the European Union (EU)", calling on the EU member states to make the fight against breast cancer a health policy priority and to develop and implement effective strategies for improved health care encompassing screening, diagnosis and treatment throughout Europe.[51] One of the items of the resolution is that the EP calls "to establish a network of certified multidisciplinary breast centres which cover the entire population". The different criteria have been further detailed and made operational by the European Society for Medical Oncology (ESMO).[52]

Among the different norms that these breast centres should meet, the norm on the minimal annual volume (i.e. at least 150 women with breast cancer treated per centre, at least 50 operations per surgeon) has generated much discussion in Belgium. This is not surprising, as at that time only 14 hospitals out of 108 fulfilled the European volume norm, and 17 treated between 100 and 150 women annually. More worrying, 44 hospitals treated less than 50 patients a year (data 2003).

Four years after the EU resolution, the Belgian legislation on the recognition of breast clinics was published (AR/KB 26th April 2007)[g], and specifies the many quantitative norms that a hospital has to meet in order to be recognised as breast clinic. A transition period was foreseen so that hospitals could reorganise their services: during the first two years, a minimal volume of 100 newly diagnosed patients per year was required. After the end of the transition period, the volume norm increased up to 150 patients per year (the EU recommendation), with an exception if there was another recognised breast clinic within a distance of 50 km, in which case the cut-off of 100 still applied. [h] In 2012, the 2 year transition period has been expanded to a 4 year transition period; in 2013, 50 hospitals were recognised as a “breast clinic” based on the transition period norms.[i] At present it is not known what the annual volume of the breast clinics "in transition" is, and more importantly, it is not known how many breast cancer patients are still being treated outside the recognised centres (which is legal as physicians working in hospitals not recognised as breast clinic are still allowed to treat patients with breast cancer).

4.5 Radiotherapy centres

Radiotherapy in Belgium is offered in 25 hospital-based centres that have been authorised for this activity (KCE report 198).[53] Eight of these centres serve one or more satellite centres, which are based in another hospital. These 25 radiotherapy centres and the 11 satellites treat about 30 000 patients/year with external photon- or electrontherapy. The Belgian compulsory health insurance provides coverage for radiotherapy treatments in these centres when performed by one of the 155 recognised radiotherapy specialists. A pilot project on the quality assurance in radiotherapy was initiated in 2010 and will last until 2014 (Action within the Belgian Cancer Plan).

When the irradiating beams are made of charged particles (protons and other ions, such as carbon), radiation therapy is called Hadron therapy. The strength of Hadron therapy lies in the unique physical and radiobiological properties of these particles; they can penetrate the tissues with little diffusion and deposit the maximum energy just before stopping. This allows a precise definition of the specific region to be irradiated. With the use of hadrons the tumour can be irradiated while the damage to healthy tissues is less than with X-rays (http://enlight.web.cern.ch/). Proton therapy, a type of Hadron therapy, is particularly useful to treat paediatric cancers owing to its potential to reduce side effects like developmental retardation and secondary cancers. Carbon therapy, another type of Hadron therapy, can be more useful in adult patients with cancers that resist to conventional and proton radiotherapy. For the Belgian context it is estimated that 223 adults and 34 children per year would meet standard indications for Hadron therapy. Adding other indications for which Hadron therapy could have an added value, increases the number of potential Belgian patients for Hadron therapy up to 1 820 patients per year.

---

g AR/KB 26.04.2007 'Arrêté royal fixant les normes auxquelles le programme de soins oncologiques spécialisé pour le cancer du sein doit satisfaire pour être agréé / Koninklijk besluit houdende vaststelling van de normen waaraan het gespecialiseerd oncologisch zorgprogramma voor borstkanker moet voldoen om te worden erkend' (MB / BS 20.07.2007).

h AR/KB 07.06.2012 ' Arrêté royal modifiant l’arrêté royal du 26 avril 2007 fixant les normes auxquelles le programme de soins oncologiques spécialisé pour le cancer du sein doit satisfaire pour être agréé / Koninklijk besluit houdende wijziging van het koninklijk besluit van 26 april 2007 houdende vaststelling van de normen waaraan het gespecialiseerd oncologisch zorgprogramma voor borstkanker moet voldoen om te worden erkend' (MB / BS 27.06.2012).

i The list of all breast clinics for 2011 is available on the website of the FPS Public Health (http://www.health.belgium.be/eportal/Healthcare/Healthcarefacilities/index.htm).

Until now, Hadron therapy is not available in Belgium, but 14 Hadron therapy centres are active in Europe, 5 of them being candidate centres for referral of Belgian patients: Orsay (Paris), PSI (Villigen, Switzerland), Munich (Germany), Heidelberg (Germany) and Pavia (Italy). The capacity in European centres is expected to double in the next 3-5 years, due to the increasing capacity of existing centres and the start of new centres in Essen, Trento, Uppsala, Marburg, Prague, Vienna and Krakow. The chance of referral to a Hadron therapy centre depends entirely on local initiatives.

Among referral systems, unidirectional referral at the local-regional level and referral/back referral at the national and international levels are the most popular models.[54] In the first model, patients stay under the responsibility of the Hadron therapy centre for the treatment and the follow-up whereas in the second model, referring centres are responsible for the follow-up.[54] Medical Excellence Japan proposed a flexible concept that solves the logistic problem of referral and back-referral on the national and international levels.[54]

However, the report of the Belgian Hadron Therapy Centre (BHTC) Foundation illustrated the difficult networking with potential referring physicians. Only a very small fraction of the potential patients have been given the opportunity to be treated with Hadron therapy abroad, due to lack of referral.[54] International experts identified the absence of a liaison function as a threat to referral/back referral of eligible patients for Hadron therapy, irrespective of the location of the centres, inside or outside the country.

5 DISPERSION OF CANCER CARE IN BELGIUM

5.1 Introduction

In order to feed the reflections on an improved organisation of care for patients with rare cancers and cancers requiring complex treatment, and to help setting priorities, an accurate overview of the actual situation in Belgium is a natural starting point. One of the important aspects of care is the number of patients managed in a certain centre or by a certain health care provider. Astonishingly, these data are completely confidential in Belgium and are put under a taboo. Hence, this crucial information remains unknown to patients who need to take informed decisions, unknown to GPs and specialists who would like to refer their patients to an experienced healthcare practitioners, and even unknown to policy makers who have the responsibility to enable optimal health care for the citizens.

This chapter has two objectives. First, it summarises the evidence of the dispersion of cancer care in Belgium, based on published reports and the analysis of recent nomenclature[j] data. Second, it summarizes published evidence on the consequences of this dispersion in Belgium, based on studies on the association between the volume of some procedures and patients' outcomes.

[j] The nomenclature is a series of codes issued by the NIHDI; every code corresponds to a certain medical act, a fee and a certain amount that is reimbursed by the health insurance. Analyses of the attested codes enables the quantitative evaluation of medical acts performed by health care providers in Belgium.

5.2 Evidence of dispersion of cancer care in Belgium

For this section three sources of information were used. First, several KCE reports illustrated the dispersion of cancer care in Belgium for some rare cancers (testis cancer,[32] oesophageal cancer,[33] gastric cancer,[33] pancreatic cancer[55]) and more frequent cancers (breast cancer,[56] colon cancer,[55] lung cancer[55]). These data are presented in Table 5. Second, a high variability in processes of care in Flanders is documented for a series of rare cancers in a recent report published by the BCR by order of the Vlaamse Liga tegen Kanker ('VLK study'[57]). These data are also presented in Table 5. Third, volume of reimbursed medical acts national claims data) per hospital were communicated by the NIHDI (RIZIV-INAMI) (Table 6).

Methodological details can be found in the above references for Table 5 and are provided in Appendix 3 for Table 6.

Table 5 – Summary of dispersion of cancer care in Belgium, results from published studies

Group of tumours	Tumour sites (patient subgroup)	Incidence timeframe	N patients (in study)	Mean number of patients/year	N hospitals (in study)	Mean annual vol./centre	Source
Head and neck	Nasopharynx	2004-2007	71 [F]	**18** [F]	15 [F]	**1.2**	VLK study
	Salivary glands	2004-2007	235 [F]	**59** [F]	46 [F]	**1.3**	VLK study
	Hypopharynx	2004-2007	384 [F]	**96** [F]	29 [F]	**3.4**	VLK study
	Larynx	2004-2007	1227 [F]	**319** [F]	55 [F]	**5.8**	VLK study
	Oropharynx	2004-2007	811 [F]	**203** [F]	46 [F]	**4.3**	VLK study
	Oral cavity	2004-2007	1077 [F]	**269** [F]	54 [F]	**4.7**	VLK study
	Lip	2004-2007	167 [F]	**42** [F]	45 [F]	**<1.0**	VLK study
Digestive	Oesophagus	2004-2008	5 813	**1 163**	112	**10.3**	KCE report 200
	Oesophagus (operated patients)	2004-2008	1 977	**395**	112	**3.5**	KCE report 200
	Stomach	2004-2008	4 847	**969**	115	**8.4**	KCE report 200
	Stomach (operated patients)	2004-2008	2 409	**482**	115	**4.2**	KCE report 200
	Pancreas (operated patients)	2004	311	**311**	74	**4.2**	KCE report 113
	Colon (operated patients)	2004	2 730	**2730**	114	**23.9**	KCE report 113
	Anal Canal	2004-2007	149 [F]	**37** [F]	36 [F]	**1.0**	VLK study
Breast	Breast	2001-2006	50 039	**8 340**	111	**75.1**	KCE report 150
Thoracic	Lung (operated patients)	2004	1 206	**1 206**	97	**12.4**	KCE report 113
	Mesothelioma	2004-2007	556 [F]	**139** [F]	49 [F]	**2.5**	VLK study
Male genital	Testis	2001-2006	1 307	**218**	97	**2.2**	KCE report 149
Female genital	Vulva	2004-2007	298 [F]	**75** [F]	54 [F]	**1.4**	VLK study
	Vagina	2004-2007	65 [F]	**16** [F]	29 [F]	**<1**	VLK study

Note. [F] *data only available for Flanders*

The analyses performed by the Belgian Cancer Registry on Flemish data (period 2004-2007) relating to the distribution of patients by hospital show a large spread in the management of patients with rare cancers. The number of hospitals in the Flemish Region taking care of rare cancers ranges from 15 (nasopharyngeal cancer) to 55 (laryngeal cancer). Such wide range might be firstly related with the large differences in incidence between the rare cancer entities (71 patients with nasopharyngeal cancer compared to 1 227 patients with cancer of the larynx). However, treatment options might also play a role for the observed dispersion: the care for nasopharyngeal cancer is probably less dispersed because the main treatment for this tumour type (radiotherapy) is not available in each hospital. Patients are unequally distributed among hospitals, and large deviations are seen between the mean and median number of patients by hospital. For example, during the 4-year observation period the 384 patients with hypopharyngeal cancer have been treated in 29 different Flemish hospitals, with a mean volume of 13.5 patients per centre, a median of 2 and a range between 1 and 56 patients per centre. Patients with vulvar cancer were managed in 54 different Flemish hospitals (mean is 5.4, median is 3, range between 1 and 42). During the same period, patients with vaginal cancer were treated in 29 different Flemish hospitals (mean 2.1, median is 2, range between 1 and 7). These data confirm that some hospitals clearly treat more patients with a certain rare cancer entity than others. For the majority of the evaluated rare cancer types, the case load per hospital is lower than 5 patients per year, and sometimes even lower than 1 patient per year (Table 5).

Due to the low number of patients diagnosed and treated in a wide variety of hospitals, the BCR was not able to analyse the variability in treatment schemes (e.g. between low- and high-volume centres) for a number of cancer types (e.g. cancer of the salivary glands, anal canal cancer, lip cancer, nasopharyngeal cancer, vaginal and vulvar cancer). For hypopharyngeal and oral cavity cancer, treatment schemes were comparable between low- and high-volume hospitals. This is not the case for laryngeal and oropharyngeal cancer and mesothelioma, for which surgery seems to be less frequently considered as the primary treatment in high-volume hospitals compared to their low-volume counterparts. This finding may be confounded by the fact that radiotherapy has been considered in the process of assigning patients to a centre.

Same dispersion of care was shown for male patients with testis cancer between 2001 and 2006 in all Belgian hospitals while evidence for digestive cancers focuses on oesophagus, stomach, pancreas, colon and anal canal. These cancers are treated in almost all Belgian hospitals, with the consequence of a very low number of patients treated annually per hospital. Colon cancer is an exception, since annual volume is a bit higher, however without reaching an average of 25 patients per year. Oesophageal surgery was performed in 64 hospitals in 2011 (Table 6) with a mean number of 7 operations per centre. The mean is however not a good indicator of the “typical” volume per hospital when the distribution of data is so skewed, as shown in Figure 4. Two centres record much larger volumes than all the other hospitals and tend to "pull" the mean upward. The median of 4 operations per year (Figure 4) represents actually the situation of a “typical” hospital in Belgium: 50% of the Belgian hospitals where at least one oesophagectomy was performed (i.e. 64 hospitals in 2011), performed no more than 4 oesophagectomies per year. As is depicted in Table 6, the situation is similar for pancreatectomy and HIPEC.

Dispersion of care for these 4 complex procedures is illustrated in Figure 4 to Figure 7.

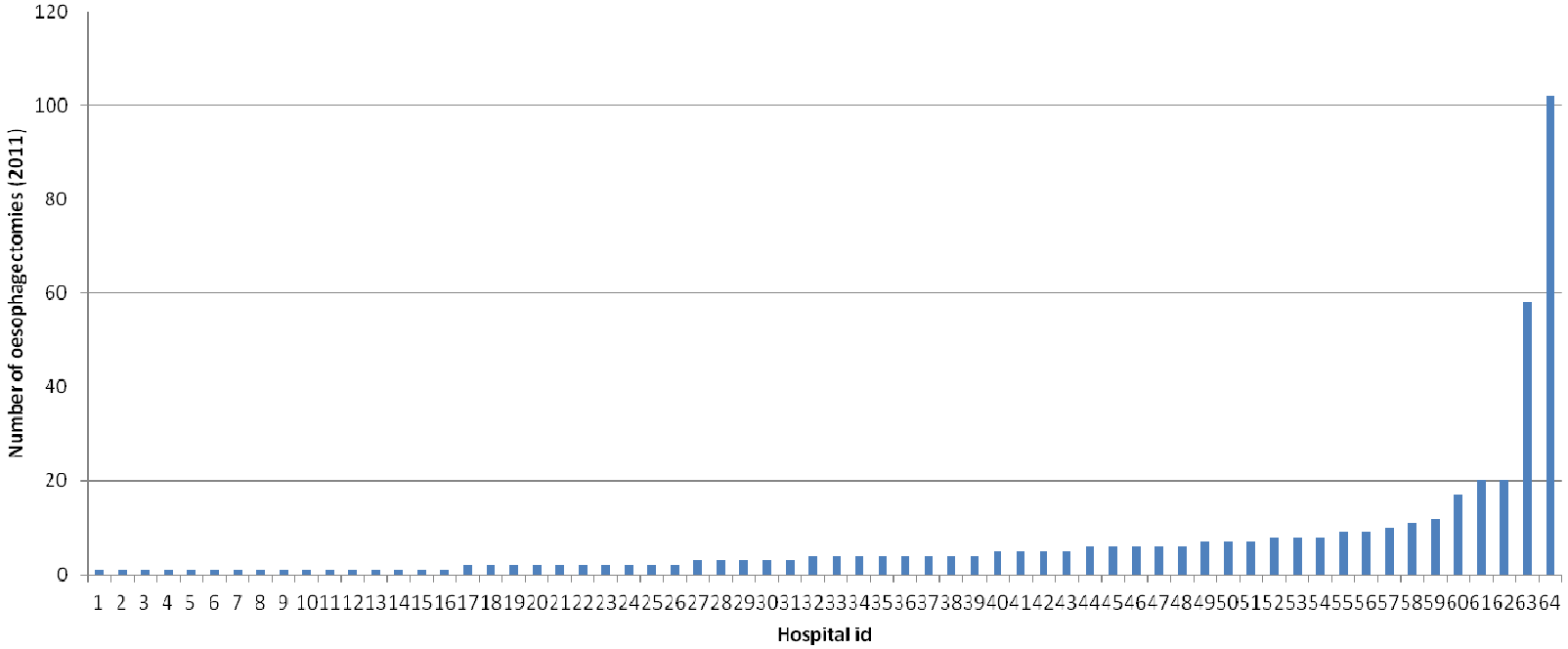
Table 6 – Summary of volume data for selected complex procedures in Belgium (2011)

Procedure	Total procedures	N hospitals	Mean volume	Median	P 75
Oesophagectomies	446	64	7.0	4	6.5
Pancreatectomies	794	91	8.7	4	8
HIPEC	123	15	8.2	4	10
Colectomies for FAP[k] patient	108	31	3.5	1	2

Source. RIZIV-INAMI data

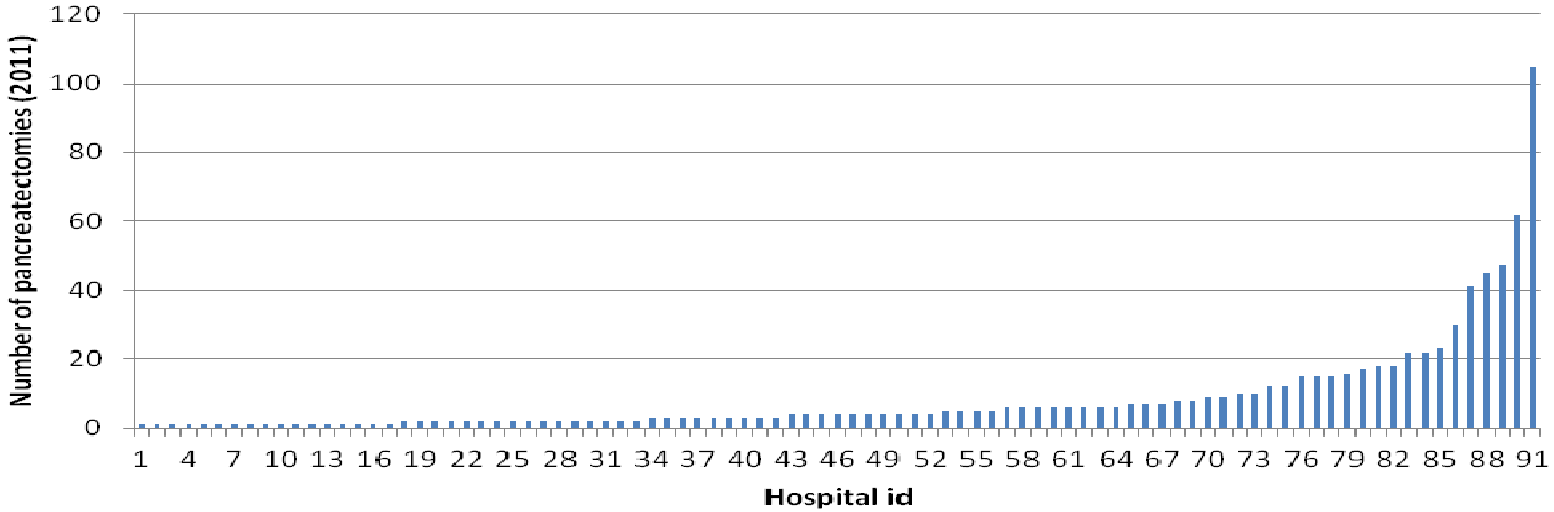
[k] Proctocolectomie ou colectomie de restauration avec construction d'un réservoir iléal, mise en place d'une anastomose iléo-anale et éventuelle iléostomie proximale temporaire / Restauratieve proctocolectomie of colectomie met constructie van een ileumreservoir, aanleggen van een ileo-anale anastomose met of zonder een tijdelijke proximale ileostomie.

Figure 4 – Distribution of oesophagectomies by hospital, in 2011



Source. RIZIV-INAMI data

Figure 5 – Distribution of pancreatectomies by hospital, 2011



Source. RIZIV-INAMI data

Figure 6 – Distribution of Colectomies for FAP[I] patients by hospital, 2011

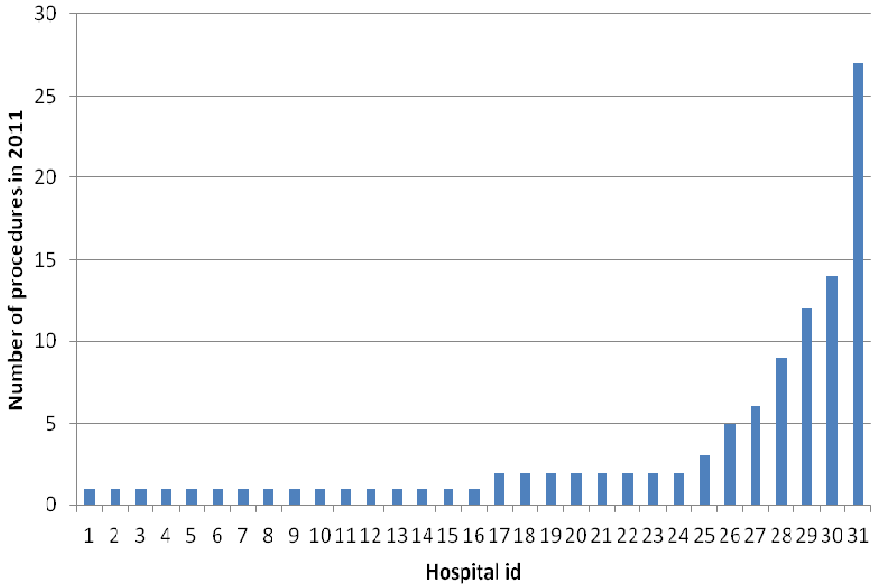
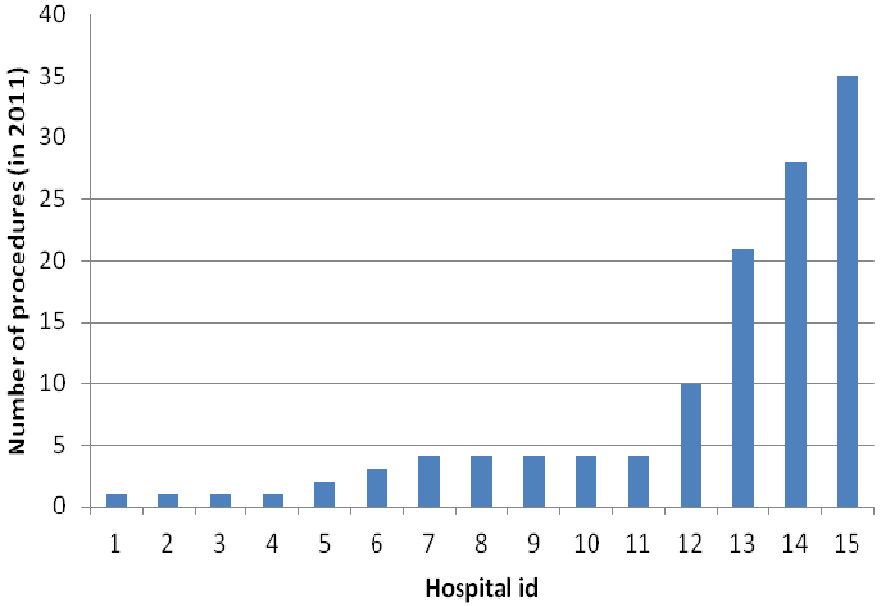


Figure 7 – Distribution of HIPEC procedures by hospital, 2011



Source. RIZIV-INAMI data

[I] Proctocolectomie ou colectomie de restauration avec construction d'un réservoir iléal, mise en place d'une anastomose iléo-anale et éventuelle iléostomie proximale temporaire / Restauratieve proctocolectomie of colectomie met constructie van een ileumreservoir, aanleggen van een ileo-anale anastomose met of zonder een tijdelijke proximale ileostomie.

5.3 Association between processes, volume and outcomes: convergence between Belgian and international evidence

The literature on measuring and explaining the association between volume and outcomes of certain surgical procedures has basically started in 1979 with the publication of Luft, who showed that, for a number of common surgical procedures, the in-hospital mortality was lower in hospitals where the operations were performed frequently.[58] This study concluded that "regardless of the explanation, the data support the value of regionalisation for certain interventions". This publication led to similar studies, extended to virtually all domains of care. In the USA, a series of famous studies, led by Birkmeyer,[59-61] demonstrated improved short and long term outcomes for high volume hospitals for a large panel of interventions. These findings resulted in the adoption of minimal hospital and practitioner volume criteria, which was imposed by associations of health consumers and health insurers (Leapfrog[m], BlueCross BlueShield Association[21]). Moreover, volume was considered a quality indicator for several complex procedures[n]. In Europe, a number of studies, mainly from the Netherlands[62-64] and the UK,[65] have reproduced some findings from the American studies. In addition, two recent Cochrane reviews (on colon cancer surgery and on ovarian cancer surgery) also confirm the positive association between volume and patient related outcomes.[66, 67]

For the appropriate execution of this type of studies, the following steps are essential:

1. A complete and reliable national cancer registry, which contains accurate prognostic variables;
2. A linkage, at the patient level, between the data from this cancer registry and mortality data from a population registry, allowing to measure long-term survival,
3. A linkage, at the patient level, between data from this cancer registry and national claims data, allowing to identify all care processes that compose the clinical pathway for each patient;
4. A clear algorithm to assign each patient to a specific centre, which is a complex process (as patients may be managed by different hospitals in function of the procedure performed, especially for radiotherapy);
5. The registration of the patient's comorbidity data (or a proxy of those);
6. A data collection covering a critical number of years, required to attain enough precision in the estimation despite the low number of annual cases (large periods have to be balanced with the need to work on recent data, large retrospective studies being frequently weakened by outdated data);
7. Approval for the data linkages by the Belgian Privacy Commission, to guarantee the legal utilisation of patient's individual medical data.

The set-up of such studies requires human and technical resources, and can take up to one year. Given these requirements, it will not be surprising that studies documenting the impact of the volume of processes of care and subsequent survival for cancer patients are very rare in Belgium, and have all been published by KCE, in close collaboration with the BCR.

In 2009, KCE published a report entitled "the volume of surgical interventions and its impact on outcomes: feasibility study based on Belgian data". The study consisted of a search of evidence in the scientific literature, and of the analysis of 12 procedures: 5 cancer surgery procedures (i.e. oesophageal, pancreatic, colon, breast and lung cancer surgery), 4 cardiovascular procedures (carotid endarterectomy and carotid stenting, coronary artery bypass graft with/without heart valve replacement or repair, and percutaneous coronary intervention) and 3 orthopaedic procedures (total hip replacement, total knee replacement and hip fracture surgery).[55] The study was merely a feasibility study, aiming at determining the appropriate methodology, testing the potential linkage of data from different sources (RCM/MKG, BCR, IMA) from one year (2004) and to test existing international minimal volume thresholds on Belgian data. Although the study confirmed an association volume-outcomes, it did not have any political impact nor a lot of media attention.

---

m www.leapfroggroup.org

n http://www.qualityindicators.ahrq.gov/Downloads/Modules/IQI/V42/Inpatient%20Broch%2010%20Update.pdf

Two more recent KCE reports and their subsequent international publications showed that high-volume hospitals adopted recommended processes of care more frequently than low-volume hospitals; this was demonstrated for breast cancer[56, 68] and testicular cancer.[32, 69] In the breast cancer study hospitals were classified according to their annual volume of treated patients: <50 (very low), 50-99 (low), 100-149 (medium) and ≥ 150 patients (high). Between 2004 and 2006, volume of care was particularly low since half of the hospitals treated less than 50 patients per year. Six of the eleven recommended process indicators were more frequently adopted in high-volume hospitals: multidisciplinary team meeting, cytological and/or histological assessment before surgery, use of neoadjuvant chemotherapy, breast-conserving surgery rate, adjuvant radiotherapy after breast-conserving surgery, and follow-up mammography. High-volume hospitals reached higher 5-year survival rates than low-volume hospitals; the 5-year observed survival rates were 74.9%, 78.8%, 79.8% and 83.9% for patients treated in very low-, low-, medium- and high-volume hospitals respectively.[68]

With regard to testicular cancer, on 1 307 patients diagnosed during 2001 and 2006 in Belgium, 1 176 underwent an orchidectomy. Of those, 40% were performed in 14 centres, while the remaining 60% was performed in 83 centres. More than one-third of the centres treating patients with testicular cancer in the study period performed a mean of one orchidectomy or less per year. This dispersion of care and the resulting low annual number of patients with testicular cancer in many centres hampers definite comparison on process indicators between centres (for five indicators a broad range of results were found across centres, mostly ranging between 0% and 100%).[69] Whereas 5-year survival is relatively high in this population (all patients considered, 94%), nine centres reached a lower 5-year observed survival than the others. All these centres treated less than 20 patients during the observation period.[69]

In 2013, a KCE report on quality indicators for upper gastrointestinal cancer (oesophageal cancer and gastric cancer)[33] illustrated, once again, that volumes of care per hospital were noticeably low in Belgium. Only 2 hospitals reached the limit of 20 interventions per year for oesophageal cancer whereas for gastric cancer, only one Belgian hospital performed at least 20 surgical interventions per year. Again, a **clear volume-outcome relationship** was found for postoperative mortality (oesophageal cancer) and 5-year survival (oesophageal and gastric cancer). In the Belgian cohort, 30-day and 90-day mortality for patients treated in high-volume centres (i.e. treating at least 20 patients per year) was 1.7% and 5.0% compared to 7.4% and 12.6% for patients treated in low-volume centres (i.e. treating <6 patients per year). The lowest mortality rates obtained by high-volume centres are very well in line with those reported in the Netherlands, where a 30-day mortality as low as 1.4% was reported in 2011,[70] after the introduction of volume criterions for the treatment of patients with oesophageal cancer.

6 INTERNATIONAL INITIATIVES AND RECOMMENDATIONS

6.1 Introduction

This chapter describes initiatives at the European level (i.e. directives, non-binding recommendations, projects and initiatives taken by scientific associations), a review of lessons learnt from a selection of European countries (see 6.3 and Appendix 5) and an initiative taken in the USA (see 6.4).

For an detailed overview of European projects on surveillance, research and organisation of care (e.g. the RARECARE project and RARECARENet, Rare Cancers Europe (RCE) - European Action Against Rare Cancers, European Partnership for Action Against Cancer (EPAAC), the Organisation of European Cancer Institute's (OECI), International Rare Cancer Initiative (IRCI), European Union Committee of Experts on Rare Diseases (EUCERD)), the reader is referred to Appendix 4.

6.2 Initiatives at the European level

Due to their low frequencies, rare cancers are difficult both for clinical decision-making and for organisation of health care. On the one hand, clinical decision-making is hampered by the lack of clinical studies leading to limited available evidence, sometimes of poor quality. On the other hand, the management of rare cancers is more problematic than for common cancers, due to a lack of clinical expertise of oncologists. Also, fewer treatments have been developed for rare cancers than for common ones. For these reasons, rare cancers are an important policy concern for public health in Europe.[9] Access to appropriate health care for rare cancers differs significantly among Member States. There is therefore considerable scope for action at the EU level, both in promoting research and in sharing the scarce available knowledge on rare cancers.[9]

At the European level the following initiatives with regard to rare cancers and cancers that require complex care have been taken; for more detailed information, the reader is referred to Appendix 4.

6.2.1 The European Directive 2011/24/EU

The **European Directive** 2011/24/EU on the application of patients' rights in cross-border health care was adopted in March 2011. This Directive aims at facilitating access to safe and high-quality cross-border health care within the European Union and establishes, at the same time, a framework for future cooperation on health care between Member States. One domain of cooperation is the development of European Reference Networks (ERNs) (Article 12) that have to improve access to and provision of high-quality health care to all patients who have conditions requiring a concentration of specialised resources or expertise and which could also act as focal points for medical training and research, information dissemination and evaluation, especially for rare diseases (Article 54).

The European Commission (EC) is required to establish a list of criteria and conditions for these ERNs as well as for providers wishing to join them. These criteria and conditions have to ensure that ERNs concentrate the required knowledge and expertise, follow a multidisciplinary and collaborative approach, and pursue activities in research and training. The ERNs should also play a specific role in the development and dissemination of good practice guidelines, expert information and in the implementation of outcome measures and quality control (Article 12.4).

Article 12 of the Directive 2011/24/EU lists the objectives and characteristics for ERNs to qualify as such. They can pursue different objectives, ranging from the improvement of diagnosis and delivery, through the pooling and sharing of knowledge and expertise, to the concentration of resources or patients (Article 12.2). The functions and features of ERNs are (Article 12.4):

1. to have knowledge and expertise to diagnose, follow up and manage patients with evidence of good outcomes, as far as applicable;
2. to follow a multidisciplinary approach;
3. to offer a high level of expertise and have the capacity to produce good practice guidelines and to implement outcome measures and quality control;
4. to make a contribution to research;
5. to organise teaching and training activities; and

6. to collaborate closely with other centres of expertise and networks at national and international level.

Before the Directive is implemented in October 2013, the EC is preparing a Delegated Act as well as implementation measures for evaluating the ERNs and facilitating the exchange of information and expertise. To support and advise the EC, a Cross-border Healthcare Expert Group was established with representatives from Member States.

The European Observatory on Health Systems and Policies was asked to produce a preliminary scoping paper to explore national practices with regard to reference networks, looking at definitions used, criteria employed, and policies and legal frameworks developed.[45] The review of national practices from 21 Member States reflects the high diversity in motivation to create reference networks, in methods used to identify centres of reference and in target populations or conditions:

- **Motivation to create reference networks:** the need to concentrate or centralise the provision of highly specialised services in a limited number of medical institutions *versus* the desire to improve clinical expertise and research on the treatment of specific (mainly rare) diseases.
- **Scope and identification of reference centres:** development of well-established systems and procedures for defining scope and designating centres and networks as well as for monitoring their activities and outcomes *versus* de facto systems, i.e. traditional position or professional recognition of some hospitals leads them to be natural leading centre without any clear criteria or quality control mechanisms.
- **Technical focus:** rare diseases versus more common and chronic conditions (e.g. cancer, diabetes).

The European Observatory on Health Systems and Policies formulates the rationale for reference centres very nicely: "Beyond the arguments of economies of scale, centralising specialised health care answers to considerations for quality, safety, accessibility, cost–effectiveness, coordination and continuity of care, and patient orientation. Establishing provider networks fits with these key concerns and is supported by convincing evidence that better quality and better outcomes are achieved if complex interventions for diagnosis and treatment are concentrated in specialised centres with a critical mass of expertise, equipment and experience".[45]

In conclusion, the European Directive on cross-border health care will certainly put an additional pressure on Member States to identify reference centres and to create networks with other existing networks throughout Europe. Another aspect of this directive is the free movement of patients ('health care tourism'). Hence, if hospitals want to be attractive for foreign patients, they will have to perform well and make their outcomes publicly available.

In the margin, it should be noted that other drivers such as insurance companies (DKV Germany, the 'zorgverzekeraars' in the Netherlands) have also developed recognition programmes to help insured members find specialty care at facilities proven to have delivered better overall outcomes. They recognise health care facilities that provide a full range of cancer care services for adults, delivered by multidisciplinary teams with subspecialty training and distinguished clinical expertise in treating complex and rare subtypes of cancer.

6.2.2 The European Recommendation 2009/C 151/02

The European Commission Communication on rare diseases and the non-binding Recommendation from the European Council (2009/C 151/02) advocated that Member States establish and implement plans and strategies for rare diseases by 2013 in order to improve equity of and access to prevention, diagnosis, treatment and rehabilitation for patients suffering from rare diseases.[13]

6.2.3 European Projects

- The **RARECARE project** (the Surveillance of Rare Cancers in Europe) has proposed a definition for rare cancers, based on incidence rather than prevalence, i.e. < 6 new cases/100 000 inhabitants/year. It also provides cancer burden indicators (incidence, survival, prevalence and mortality), based on population-based cancer registry data, on rare cancers across Europe.

- Building on the experience of the previous project **RARECARE** and, in collaboration with **Rare Cancers Europe (RCE)** and others, **RARECARENet** aims at building an information network to provide comprehensive information on rare cancers to the community at large (patients, oncologists, general practitioners, researchers, health authorities). The final objectives are to improve the timeliness and accuracy of diagnosis, to facilitate the access to high quality treatment for patients with rare cancers, to identify centres of expertise for rare cancers in Europe and to standardize practices across Member States.

  Six specific objectives are pursued that come in different work packages. The fifth Work Package **'Information on centres of expertise for rare cancers'** aims at identifying qualification criteria for centres of expertise for rare cancers. Following the approach to define general criteria for European Reference Network for rare diseases, **a list of criteria indicating the level/quality of expertise** for rare cancers management will be developed in collaboration with multidisciplinary experts of the major scientific societies, patients' organisations and policy makers.

  For a selected subgroup of rare cancers, more specific indicators will be collected through high resolution studies in a sample of countries. Cancer registries will be requested to collect clinical information on staging procedures, treatment, recurrence, multidisciplinary teams etc. During face-to-face meetings possible criteria indicating the level/quality of expertise for rare cancers management will be discussed.
- The **European Partnership for Action Against Cancer (EPAAC)**, an initiative under the umbrella of the European Commission, aims at improved collaboration between countries in the field of national cancer control policy. Several work packages have been launched; work package 7 will have a particular focus on new organisational perspectives in cancer care, specific networks at regional level and low frequency cancers.
- The **Organisation of European Cancer Institutes - European Economic Interest Grouping** (OECI-EEIG) aims at improving the quality of cancer care and translational research in Europe from an organisational viewpoint. Four working groups are conducting focused expertise projects among which the Accreditation/Designation Working Group. Based on a self-assessment survey and a peer-review visit by the OECI, cancer centres who apply (and pay) for it, can receive the accreditation of a Comprehensive Cancer Centre or a Clinical Cancer Centre. So far, no specific norms per cancer type have been developed by OECI.
- The **International Rare Cancer Initiative** (IRCI) aims at facilitating the development of international clinical trials for patients with rare cancers, in order to boost the progress of new treatments for these conditions.

Belgium is actively involved in all these initiatives, owing to the participation of the Belgian Cancer Registry, the Cancer Centre and the FPS Public Health.

Note

The work of **The European Union Committee of Experts on Rare Diseases** (EUCERD) did not focus on rare cancers but more globally on rare diseases. However, it needs also to be mentioned here, because it was used as a source of inspiration for rare cancers. This Committee is charged with the surveillance of initiatives and incentives in the field of rare diseases at a European level and at the member state level (http://www.eucerd.eu/). EUCERD decided to concentrate its activities on the **organisation of expertise** at a national level including the following topics:

- the models of **organisation of expert care** at a national level according to country size (health care pathways versus a system of coordinating centres and expert centres);
- defining the **scope of expert centres** in terms of disease coverage and links with university hospitals and medical specialties including reflections on recommendations for organisation by size of country;
- **quality designation criteria** for national centres of expertise for rare diseases in view of the experiences of the Member States.

EUCERD concluded that national centres of expertise for rare diseases should provide healthcare services to patients with conditions requiring a particular concentration of resources and/or expertise, provide cost-

effective, high quality care and provide focal points for medical training and research, information dissemination and evaluation. Different criteria were proposed to designate national centres of expertise and it was agreed that the designation process at country level can either follow a **"bottom-up" model**, through a call for proposals, or a **"top-down" model**, through a public health plan.[71, 72] The "bottom-up" model was considered more pragmatic whereas the "top-down" approach more ambitious.

6.2.4 *Initiatives taken by European scientific societies (ESMO)*

Following the observation that sub-optimal treatment outcomes were relatively common for rare cancers due to a lack of medical expertise in the management of rare cancers, poor referral rates from general practitioners and pathologic misdiagnosis, the representatives of the European Society for Medical Oncology (**ESMO**) elaborated a set of 39 recommendations on stakeholder actions and public policies in order to improve rare cancer care in Europe.[73]

These recommendations can be grouped into 6 areas:

- **Regulatory barriers in rare cancer care**: rethinking study designs and statistical analyses for the evaluation of rare cancer therapies since low incidence rates make well-powered RCTs infeasible, decisions on the use of new agents in rare cancers, involvement of HTA agencies (e.g. involvement of patients and stakeholders, input from expert oncologists in rare cancers);
- **Methodological barriers to rare cancer care**: more clinical trials, testing of new agents in rare cancer patients, encourage network-based clinical databases, funding of clinical studies, other approaches for statistical analysis, acknowledgement of the informed patient;
- **The need for centres of expertise and European reference networks**: consensus guidelines on multidisciplinary treatment, exchange of experience, integration of local, national and European centres of expertise into European reference networks, harmonisation of quality criteria for reference centres, funding and resources. Referral to centres of expertise is crucial, especially with regard to timely diagnosis and correct clinical decision-making on an overall therapeutic strategy.
- **Barriers to patients' access to care**: solidarity, equity, EU transparency directive, development of medicines, risk management strategy, patients' rights in cross-border healthcare, collaborative networks of centres of expertise;
- **Education of health care professionals**: improved education and on-going training, raising awareness about rare cancers, especially the need for referral for specialist intervention or a second opinion;
- **Access to information on rare cancers**: wide-spread dissemination of information on treatments and how to access expert treatment and care, addressing linguistic barriers.

The ESMO political recommendations are the result of the joint work of the research community, healthcare professionals, EU policy-makers and regulators, patients and industry representatives before, during and following the ESMO Conference on Rare tumours in November 2008 in Brussels. With this initiative ESMO is seeking to put rare cancers firmly on the European policy agenda. The aim of the recommendations is to raise awareness about the issues surrounding rare cancer care and to suggest stakeholder action and public policies both at the EU and national levels as possible routes to solutions.

6.3 Lessons learnt from European Member States

The present chapter provides an overview of some European Member States' initiatives to improve the organisation of care for patients with rare/complex cancers; information was gathered up to the end of 2013.

Methods

Member States were selected based on their involvement in European projects on rare cancers, on suggestions of Belgian stakeholders, but most importantly, on the availability of sufficient information in English, French or Dutch. Several websites and official documents (e.g. European Partnership for Action Against Cancer (EPAAC), European Union Committee of Experts on Rare Diseases (EUCERD)) were consulted; reports and papers on rare cancers, reference centres and centres of excellence were systematically searched for. In addition, a range of stakeholders in each Member State have been consulted to obtain

additional informal documentation. Still, the reader should bear in mind that the information provided is not exhaustive.

All these conditions restricted the range of targeted countries to four: France, the Netherlands, United Kingdom/England and Denmark. For the other European countries no information could be obtained on their organisation of care for patients with rare cancers, either because it was not a current issue or because the information was not made available in English, French or Dutch documents. For an overview per country, the reader is referred to Appendix 5.

In order to improve the validity of this chapter and the accompanying appendices, they were reviewed and approved by experts from the respective countries: Frédérique Nowak (Head of the Innovation Department, National Cancer Institute, France), Sabine Siesling (Senior researcher, Comprehensive Cancer Centre the Netherlands (IKNL), the Netherlands) and Helene Probst (Chief Physician/Section Head of the Danish Health and Medicines Authority (Sundhedsstyrelsen), Denmark). Despite several attempts, we did not succeed in getting any feedback from the English National Health Service.

Objectives of National Cancer Plans with regard to rare/complex cancers

Inspired by National Cancer Plans or confronted with higher cancer mortality rates than adjacent countries, several European Member States have taken initiatives to improve the quality of care offered to patients with rare and complex cancers. In some European countries, “rare cancers” are covered within the framework of a national plan for cancers, in others they are included in strategies for rare diseases. Across borders, several adopted measures pursue comparable objectives, i.e.

- Facilitate early diagnosis and timely referral to centres of expertise
- Enable a multidisciplinary care approach
- Concentrate human and technical resources
- Ensure a sufficient volume of patients with rare/complex cancers to increase experience and expertise
- Create networks within the country as well as networks with bordering countries
- Use costly technology efficiently
- Increase teaching and training possibilities
- Concentrate research in centres of expertise
- Deliver adequate information to patients

More specifically with regard to rare cancers and cancers that need complex care, it has been agreed that it is impracticable, inefficient and unethical that every hospital and every practitioner offers care for every rare cancer.

Structural and organisational actions

In order to improve the organisation of care for patients with rare and complex cancers, several structural and organisational actions have been implemented:

- **Centres of expertise – Reference centres**: Some European Member States, including those four retained for this report, have designated centres of expertise for rare cancers, either in the context of a national plan for rare cancers or for rare diseases, either within the context of their current structure of healthcare delivery (e.g. Finland, Norway, Sweden, Germany, Lithuania, Estonia, Greece). Some countries like France and the United Kingdom, have regional centres of expertise for rare cancers covering the national territory, whereas the Netherlands adopted a more centralized approach at the country level. Denmark has two levels of specialised function hospitals: at the national level they are called highly specialised functions (1-3 places in the country) and there are regional function hospitals.
- **Agreements and reference networks**: In France, the management of patients affected by a given group of rare cancers relies on regional or interregional expert centres that cover the whole national territory, and are coordinated at the national level by a single national expert reference centre under the supervision of a single coordinating clinician. Each national reference centre must set up a network with regional centres of excellence. In England, the 28 NHS Cancer Networks bring together the providers of cancer care (organisations that deliver cancer services to patients) and the commissioners of cancer care (organisations that plan, purchase and monitor cancer

services) to work together to plan and deliver high quality cancer services for a specific population. In the Netherlands national agreements have been adopted on task allocation, concentration and spread of care with regard to a number of specialties and tumour types, but for many other tumours and complex diagnostic or therapeutic treatments, no national agreements have been made. In Denmark, the legislation gives the Health and Medicines Authority the right to decide on specialised functions and to approve the instalment of functions.

- **Combination of expertise and proximity**: In France, each patient affected by a rare cancer can benefit from the management in the institution of his/her choice, but being assured of high quality care from diagnosis to follow-up. This is enabled by the close networks between national reference centres and regional and interregional expert centres (cfr. supra). In Denmark the political environment has agreed that quality and expertise are more important than proximity. Yet, there are up to 3 Danish hospitals assigned as highly specialized function hospitals even when the yearly case load is less than 50 patients within the country. This is done to ensure a certain level of treatment proximity for the patient and it is also the result of the fact that other criteria than volume, such as complexity of disease and resources, are taken into account when deciding in how many hospitals a certain specialised function should be installed. Hospitals that are not approved to carry out a certain function, are actually not allowed to perform these. The NHS Cancer Networks in England were also chosen to reflect existing geographical patterns of referral and joint care for cancer patients. They cover populations varying between a half and 3 million people, and roughly following local administrative boundaries. In the Netherlands, the guarantee of expertise is overarching the principle of proximity. The leitmotiv of the Dutch Federation of Cancer Patients' Organizations (Nederlandse Federatie van Kankerpatiëntenorganisaties, NFK) is "Kankerzorg dichtbij als het kan, verder weg als het moet". The most striking example is the concentration of paediatric oncological care in 1 centre (in Utrecht) from 2016 on. To compensate for long distances between home and expert centres, families of (seriously) ill children can stay for a small charge in Ronald McDonald houses, which are situated in the neighbourhood or on the premises of certain hospitals.
- **Differentiation**: In England, the hospitals were assigned through a “top-down” decision approach, one of the three levels of care: (1) Primary care, (2) Cancer Units in district general hospitals (designated to deal with referrals from primary care and with the diagnosis, staging, and management of patients with common cancers) and (3) Cancer Centres designated to provide expertise in the management of all cancers, including common cancers and less common cancers by referral from Cancer Units. Also in Denmark, the hospitals were assigned (with regard to cancer care) through a “top-down” approach one of the three levels of care: (1) Main function (not assigned as a specialty function), (2) Regional function (can be assigned to 1-3 hospitals in each of the 5 Danish regions) and (3) Highly specialized function (can be assigned to 1-3 hospitals in the entire country). Hospitals can receive this designation for a 3-years’ period. However, if they do not fulfil the application criteria during the 3-years’ period, the approval can be withdrawn. In the Netherlands highly specialized clinical care (“topklinische zorg”) is concentrated in eight university medical centres (UMCs). These UMCs treat tertiary referral patients (“topreferente patienten”), i.e. patients with rare and complex pathologies who need highly specialized multidisciplinary care. Aim is to concentrate specialized care, research, education and training at the highest level; the less complex parts of care are performed in local shared care centres.
- **Strict criteria for eligibility of Reference centres / Centres of expertise**: In France, only teaching hospitals authorized for the treatment of cancer (i.e. 'Centre Hospitalier Universitaire' (CHU) and 'Centre de Lutte Contre le Cancer' (CLCC)) are eligible as national reference centres. The applications to be certified as national reference centres are subjected to a double expert assessment, involving international experts. For the regional or interregional expert centres the criteria for selection include multidisciplinarity, activity in relation to rare cancers, involvement in research and publications. In the Netherlands, the SONCOS (“Stichting Oncologische Samenwerking”, Foundation of Oncological Collaboration) report

describes quality standards for 21 cancer treatments in adults, including rare and more common cancers. It is a living document that will be adapted on a yearly basis. In Denmark, candidate hospitals for a specific cancer type follow an application process delivered by the Danish Health and Medicines Authority. They have to prove that they can ensure a care continuum, including surgery, chemo and/or radiation therapy. In England, specialist cancer services are only commissioned if they are already compliant, or if they have demonstrable plans to be compliant within agreed timeframes, with the NICE Improving Outcomes Guidance (IOG). For example, it is expected that providers are fully engaged in the national peer review process, and are working towards full compliance with the necessary specialist cancer standards.

- **Volume criteria**: In England, a minimum caseload was defined based on the size of the population covered by a network in order to maintain expertise and experience. Volume norms are also described in the GCP guidelines of NICE. In Denmark, volume is only one of three criteria (together with complexity and resource use) used to determine hospital designation. In the Netherlands, volume of surgical interventions is considered a surrogate for high-level processes of care. Consequently, centralisation of care is now mandatory for different cancers, whatever their incidence. In addition, volume criteria have also been defined for non-surgical treatments (e.g. melanoma, neuro-endocrine tumours), for specific cancer stages (e.g. metastatic disease) and for non-cancer therapies. Hospitals that do not qualify are not reimbursed.
- **Multidisciplinary treatment planning meetings:** In France, multidisciplinary treatment planning meetings (MDT) are organised at the regional/interregional level as well as at the national level. The regional MDTs represent the first expertise level whereas the national MDT is a second expertise level, to resolve specific difficulties (e.g. rare cancer cases, patients in whom the cancer progresses). Interactive forums (e.g. web conference) enable European experts to participate in the discussions. In Denmark, multidisciplinary treatment planning meetings have also been implemented as part of the national Cancer Patient Pathways.
- **Clinical guidelines and care pathways**: In France, clinicians involved in centres of expertise actively participate in the development of clinical guidelines for the management of patients with rare cancers. These guidelines are posted on dedicated websites (e.g. sporadic and hereditary malignant endocrine tumours on the website of RENATEN). In 2011, seven rare cancers had been covered by such guidelines. In the Netherlands and England, the Comprehensive Cancer Centre (Integraal Kankercentrum Nederland, IKNL) and the National Institute for Health and Care Excellence (NICE) respectively are in charge of the composition of clinical practice guidelines. IKNL looks at the content as well as at the organisational aspects of the care pathway. In the Netherlands, many national multidisciplinary tumour working groups in oncology were installed in order to develop more cohesive plans. In England, Clinical Reference Groups are tasked with developing service specifications and policies to ensure compliance with the NICE Improving Outcomes Guidance for rare cancers. All providers are expected to formally adopt, within their own clinical governance processes, the locally agreed pathways, policies and clinical guidelines in the Strategic Clinical Network to which they are affiliated. In addition, providers are required to provide seamless care across organisational boundaries, throughout the whole care pathway. In Denmark, 32 cancer pathways, for common as well as for rare cancer types, have been established by working groups which comprised representatives from all relevant medical societies including general practitioners, oncologists, pathologists and radiologists, together with specialists from the medical fields relevant to the specific cancer, the Danish Multidisciplinary Cancer Groups (who had a tradition of formulating clinical guidelines), nursing colleges and medical representatives from all five health regions. They cover the full care continuum, starting from a reasonable suspicion of cancer, over diagnosis and treatment up to follow-up. They all describe standard timeframes for the various elements involved in the pathway, in order to avoid unnecessary delays. Each rare cancer patient has a person assigned as a coordinator to ensure a smooth patient centred process. The highly specialized department also takes care of follow-up and control visits.

- **Research**: In France, all national expert centres are involved in fundamental, translational or clinical research on rare cancers; various expert centre coordinators are also engaged in international research projects. In parallel, other centres for early phase clinical trials were recognized in order to facilitate access to innovative treatments and their evaluation in early phase clinical trials. Both structures facilitate the inclusion of patients in clinical trials with very short delays, also for patients with very rare cancers. In Denmark research can be carried out on all levels of the health system.
- **Quality improvement and quality control**: In France, apart from databases containing incidence and follow-up data, quality indicators are developed to compare results obtained by the centres of expertise (e.g. rate of surgical re-interventions for R1; delay between diagnosis and discussion in multidisciplinary treatment planning meetings). Also external audits assess the quality of medical data recorded. In the Netherlands a variety of instruments, such as guidelines, visitations and accreditations, outcome registration, case mix adjusted feedback and quality improvement projects is used by the involved parties (i.e. care professionals, professional associations, Comprehensive Cancer Centres (Integraal Kanker Centrum, IKC), the Health Care Inspectorate (Inspectie voor de Gezonheidszorg, IGZ), health insurance companies and patients' associations) to improve the quality of cancer care.
- **National anatomopathological reference networks**: In France, the set up of anatomopathological reference networks enabled the double reading of anatomopathological specimens of some rare cancer groups (i.e. soft tissue and visceral sarcomas, malignant pleural mesotheliomas, rare peritoneal tumours, sporadic and hereditary malignant endocrine tumours in adults and lymphomas). The double reading resulted in 11% of cases (1 634/14 318 specimens) in an altered treatment plan and for another 7% (981/14 318 specimens) the diagnosis was adapted.
- **Information for patients:** In the Netherlands and France, several expert centres have set up websites that diffuse up-to-date information to care providers, patients and all other interested; this is realised thanks to the involvement of patients' associations. The majority of centres of expertise have a close link with patients' associations, who are also actively involved in the development of research protocols (e.g. patient information to obtain informed consent). In Denmark, every patient is assigned a personal coordinator, who ensures a smooth patient centred process. In addition, the e-health platform gives every involved care provider access to every detail of the care pathway, no matter where the care is provided.
- **Patients' associations:** Several rare cancer patients' associations try to provide a gateway, directing patients to further avenues of specialized care, information and support. In addition, in the Netherlands the Dutch Cancer Society (Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding) has a website and telephone help line for patients in need for help, support or information; on the website "SIB op maat" (SIB stands for "samenstellen informatie over bijwerkingen" – compose information on side effects) health care professionals as well as patients can find information on standard treatment plans, the side effects of oncological treatments and concrete advice. The Dutch Federation of University Medical Centres (NFU) has developed a special website where patients and care providers can identify the appropriate reference centre for their pathology (http://www.nfu.nl/trf/.).

Final considerations

To determine which providers and which centres are eligible for the care of rare cancer patients, the designation process can follow one of the following models: through a call for proposals (bottom/up), or a public health plan (top/down).[71, 72] When a network of reference centres is elaborated, a sound balance between high quality of care and proximity of care should be envisaged.

The European Member States' initiatives for the organisation of care for patients with rare and complex cancers demonstrate several **assets**:

- The set-up of reference networks between reference centres and affiliated hospitals improves the referral of patients and the mutual confidence in involved professionals' expertise;
- Integrated networks create additional value through harmonization of working procedures, uniformity of grading and typing of cancers and standardization of protocols and results within the network;
- Both high quality care and proximity are enabled by the set-up of reference networks;
- Differentiation of hospitals may lead to concentration of specialized care, research and training at the highest level;
- Hospitals/Expert teams have to meet strict criteria for eligibility to become a reference centre;
- Regular evaluation of quality indicators guarantees persevered efforts to maintain high-level care;
- Volume criteria are set up to maintain expertise and experience in a limited number of centres;
- Patients' medical files are more standardized and comprehensive after discussion at multidisciplinary treatment planning meetings;
- Several instruments, such as guidelines, audits, accreditation systems, feedback after visitations and quality improvement projects contribute to the improvement of the quality of care;
- Concentration of patients with rare cancers enhances the set-up of clinical trials and may improve access to innovative treatments;
- The double reading of anatomopathological data offers the confirmation or the re-orientation of the diagnosis, especially for very rare forms of cancers or for those requiring highly technical procedures;
- The diffusion of up-to-date information for patients and primary care providers is important;
- The close collaboration between reference centres and patients' associations allows reducing patients' unmet needs.

The European Member States' experiences also illustrate some **limitations**:

- In spite of well designed initiatives to improve the organisation of care for patients with rare cancers, the implementation may be inconsistent (e.g. when guidance in service reconfiguration is not properly followed, when established cancer centres turn out to be too small), which may result in perpetuating variations in service quality.
- The high specialization and centralization of care may lead to increased demand (and hence longer waiting lists) for trained site-specialists, although this might be overcome (as in Denmark) by legislation that determines maximum timeframes.
- When quality controls (e.g. audits and accreditations) remain informal and/or confidential, their impact is limited. Failure to meet standards or observe agreements has only minor consequences, when the only ones who are made aware of shortcomings and areas for improvement are the care professionals directly concerned. This is different when one has to give account to the public.
- Early diagnosis and appropriate referral of rarer cancers are a challenge for the primary health care setting, but may be improved with the implementation of pathways that describe clear referral criteria (including pathway for patients with uncharacteristic symptoms).

6.4 Initiative taken in the USA

The Blue Cross and Blue Shield Association is a national federation of independent, community-based and locally operated insurance companies. They provide healthcare coverage for nearly 100 million inhabitants. Recently, they developed a recognition programme in collaboration with the National Comprehensive Cancer Care Network and with input from a national panel of expert physicians. This programme recognises health care facilities that provide a full range of cancer care services for adults, delivered by multidisciplinary teams with subspecialty training and distinguished clinical expertise in treating complex and rare subtypes of cancer. These hospitals are certified as **Blue Distinction Centers for Complex and Rare Cancers**.

The goals of the recognition programme are to raise the quality of care delivered nationwide and to help consumers find specialty care at facilities proven to have delivered better overall outcomes. The programme focuses on the following 13 malignancies: acute leukaemia (inpatient/nonsurgical), bladder cancer, bone cancer, primary brain cancer, oesophageal cancer, gastric cancer, head and neck cancers, liver cancer, ocular melanoma, pancreatic cancer, rectal cancer, soft tissue sarcomas, medullar or anaplastic thyroid cancer.

The criteria used to select expert centres address structure, process, and outcomes of care with emphasis on subspecialty and multidisciplinary care team experience in treating complex and rare cancers as well as measures of the overall cancer programme. The recognised facilities have proven that they have experience in performing specialty procedures and have to demonstrate consistent quality in several aspects of care: delivery of care, patient safety, favourable overall outcomes and reduced complications rates.

All facilities must re-apply for the designation on a regular basis (typically every 18 - 36 months) to ensure consistent quality among facilities that have earned the Blue Distinction designation. Requirements for ongoing participation may evolve as the programme matures, but will include evaluation of quality indicators in the areas of structure, processes and outcomes.

The Blue Cross and Blue Shield Association focused on rare cancers because the volume of these cases is so low that treatment and outcomes for these cancers can vary greatly by physician and by health care facility. However, Blue Cross and Blue Shield companies anticipate expanding the list of facilities as well as developing future designations for facilities that treat more common forms of cancer.

7 ORGANISATION OF CARE AROUND REFERENCE CENTRES IN BELGIUM

7.1 Introduction

In 2002 the Hospital Act[o] introduced the possibility to designate a hospital as ‘centre of reference’. Article 14 of the same Hospital Act envisaged the specification of characteristics for designating reference centres. When the Minister of Health considered the implementation of this article in 2005, the National Hospital Council formulated a negative opinion, highlighting significant obstacles, such as the lack of a clearly defined role for teaching hospitals, the risk of the criteria being rejected, and the potential negative effects on the existing collaborations between hospitals. As a systematic quality monitoring system for care processes is still lacking in Belgium, no tool allows to verify the expertise present in self-declared expert centres, which may simply justify their excellence by the acquisition of specific highly specialised equipment or innovative technologies.[45]

7.2 Existing reference centres in Belgium

7.2.1 Reference centres for rare and chronic diseases

Currently, specific reference centres focusing on a couple of **rare diseases** have been recognised in Belgium: centres for human genetics (n=8), reference centres specialising in neuromuscular disorders (n=6), refractory epilepsy (n=4), cystic fibrosis (n=7) and rare monogenetic hereditary metabolic illnesses (n=8). In addition, some centres specialised in the treatment of **chronic diseases**, such as AIDS, chronic breathing disorders, chronic fatigue syndrome, chronic pain, autism, brain paralysis or cerebral palsy and spina bifida have also been recognised as reference centre through specific agreements (called ‘conventions’) with the National Institute for Health and Disability Insurance (INAMI/RIZIV); these agreements are regularly re-negotiated.

[o] La loi coordonnée sur les hôpitaux et les autres établissements de soins / De wet betreffende de ziekenhuizen en andere verzorgingsinrichtingen.

Although rare diseases are different, the average additional cost / patient / year is in a similar bracket (1 500 to 2 500 Euro / patient /year). The convention pays this sum (quarterly or annually) to the reference centre for every patient who receives regular treatment. Reference centres have to reach a well defined caseload (e.g. 25 or 50 patients a year), which means that if a centre does not reach the threshold, the convention does not pay for any patient.[6]

Reference centres are selected through spontaneous applications or calls. Selection criteria encompass the multidisciplinary approach, the expertise of the hospital's team members, the volume of patients treated and monitored, as well as the geographical distribution and networking with local providers. Such criteria are established by specialists and adopted by the NIHDI's college of medical directors.

The convention agreements delineate the whole therapeutic project, including the target patient group, the composition of a multidisciplinary healthcare team and the package of care. Many of these agreements are developed ad hoc, often at the centre's request, without any systematic quality assessment, audit nor control.[45] Further, it is important to mention that the contact details of the above mentioned reference centres are easily available for patients, GPs, families and others so that they know where they can get optimal care (see "Rare Diseases Organisation Belgium" (RaDiOrg, http://www.radiorg.be/homepage).

The Fund for Rare Diseases and Orphan Drugs proposed three structures to combine national expertise while encouraging networking at a European level: Centres of Expertise (CE), Centres for Human Genetics (CHG), and a Liaison network for Rare Diseases (LRD):

- The **Centres of Expertise** would be required to develop, implement and promote best practice guidelines for diagnosis and treatment, enrolling patients into a national register, creating networks with both local providers and European centres, developing training and research, and interacting with patients' organisations and the media. These Centres should be responsible for the global disease management of the patient in a multidisciplinary environment. This includes not only the medical and paramedical treatment, but also the social aspects. Care coordinators would ensure a link between the patient and all care professionals, both within and outside the Centre of Expertise. These Centres have to network with peripheral services (e.g. reporting to GPs, setting up of co-treatment schemes with peripheral specialists and peripheral hospitals, home care), with other expert centres (e.g. Centres of Expertise, Centres for Human Genetics, the Liaison Network for Rare Diseases) and with European and international expert centres.
- The **Centres for Human Genetics** (CHG) have specific expertise in diagnosing rare diseases with a genetic background and in organising genetic counselling. These Centres are expected to apply, within the framework of a future Belgian Plan for Rare Diseases to become Centres of Expertise for those rare diseases or groups of rare diseases for which they have recognised expertise (possibly in partnership with other medical experts at their hospitals). The Centres for Human Genetics will be asked to create and/or reinforce functional networks with the existing conventioned Reference Centres and the newly started Centres of Expertise and the Liaison network for Rare Diseases at their hospitals and in their region.
- The **Liaison centres Rare Diseases** (LRD) should form a network of diagnostic and treatment units performing a multidisciplinary rare disease consultation coordinated by a medical liaison officer for rare diseases. LRDs are also responsible for the follow-up and monitoring of patients who cannot be diagnosed or treated in a Belgian Centre of Expertise. Consequently, patients suffering from rare diseases for which no expertise is available in Belgium, would be referred to liaison centres for multidisciplinary consultation and eventually to a centre of expertise elsewhere in Europe. The Plan also proposes a set of accreditation criteria for these centres, which would replace the current reference centres accredited under the health insurance system.

For Belgium it is estimated that 60 000 to 100 000 inhabitants are affected by a rare disease, which corresponds to 0.57 to 0.95% of the total population.[3] The purpose is to treat 5 years after the implementation of the first measures approximately 15 000 patients in Belgian Centres of Expertise and 3 000 patients in such Centres abroad. These numbers are on top of the 3 000 to 4 000 patients who are currently treated in the Reference Centres and the 10 000 patients who are yearly seen in the Centres for Human Genetics. Furthermore, it is expected that the LRD network will yearly see approximately 2 000 patients for a multidisciplinary rare disease consultation.[6]

7.2.2 Accreditation programmes

A lot of hospitals have already taken the initiative to have the quality of their general services validated by external institutions, accredited by the International Society for Quality in Health Care (such as the Netherlands Institute for Accreditation in Healthcare and Joint Commission International). In the area of oncology, cancer centres which provide comprehensive services in supportive and palliative care as part of their routine care can voluntarily apply to receive the ESMO recognition as an "ESMO Designated Centre of Integrated Oncology and Palliative Care". This accreditation programme was initiated in 2003 and 6 Belgian hospitals received this accreditation so far. Any oncology department or cancer centre can apply, whatever its size. The criteria for accreditation, based on recommendation from the World Health Organisation (WHO) guidelines on the provision of palliative care for patients with cancer reflect the issues of integration, credentialing, service provision, research and education (see http://www.esmo.org/Patients/Apply-to-Become-an-ESMO-Designated-Centre; accessed on June 12nd 2013).

At present Belgian hospitals with a lot of experience in oncological care for adults, have no opportunity to have this expertise valorised by official recognition or certification systems. As a result, every hospital can promote itself as a self-declared reference centre in oncology, based on criteria that are never checked. In addition, there are no financial or other incentives for hospitals to apply for accreditation or to have their care processes audited.

7.3 Reference centres in oncology: Stakeholder consultation

7.3.1 Purpose

The purpose of this section is to summarise the opinions, suggestions, concerns and perceived obstacles expressed by the stakeholders invited for their feedback on this project as they are involved in the organisation of care, the delivery of care or the advocacy of patients with rare/complex cancers. Their opinions were first structured around different topics, and in a second step, a SWOT analysis (i.e. an analysis based on the strengths, weaknesses, opportunities and threats) was performed.

7.3.2 Methods

The stakeholders were invited twice to have a thorough discussion on the organisation of care for patients with rare and complex cancers. During the first meeting (June 2013), the scope, purpose and main steps of the project were presented. Afterwards, the stakeholders were invited to reply in a written form to a list of 5 questions on the current organisation of care for patients with rare and complex cancer, and on an improved organisation of care around reference centres. The questions asked were:

- What is the position of your organisation/association with regard to the organisation of care for patients with rare/complex cancers?
- What is your organisation/association's vision about an optimal organisation of care and how to implement it?
- What are the pros and cons?
- What are the limits, the obstacles, the points of attention?
- Any other considerations?

In September 2013 the summarized written replies and a first draft of the SWOT analysis were discussed during a second meeting with the stakeholders. Subsequently, the document was adopted and completed with the additional comments and forwarded to all stakeholders for their final comments.

The following stakeholders were invited and provided (oral and/or written) feedback (Table 7).[p] The list of participants is provided in Appendix 6.

All precautions have been taken by the KCE team to transcribe faithfully the opinions of the stakeholders expressed during formal meetings or in their written forms; even when ideas were not shared by all stakeholders they may have been adopted in the following paragraphs. As stakeholder meetings only deliver fruitful discussions when the group is not too large, it was impossible to obtain a group of stakeholders that would represent the entire Belgian situation. As a consequence, it was not felt meaningful to add to each remark or suggestion the proportion of stakeholders that shared a certain idea. Last but not least, it should be underlined that the following paragraphs summarise the ideas expressed by the invited stakeholders, which may not necessarily correspond to the ideas of the KCE team.

[p] The following stakeholders were invited to participate but did not provide any feedback: Ligue des Usagers des Services de Santé (LUSS), zelfhulpgroep voor Hodgkinaandoeningen, Association de patients atteints de tumeurs cérébrales, Santhea.

Table 7 – Invited stakeholders

Main actors	Name
Patient representatives	• Vlaamse Liga tegen Kanker (VLK)
	• Fondation contre le Cancer/ Stichting tegen Kanker
	• Association of patients with NET (neuroendocrine tumours) and MEN (multiple endocrine neoplasia)
	• CMP Vlaanderen: Association of patients with multiple myeloma (MM) en waldenströms macroglobulinemia (WM)
	• Werkgroep hersentumoren
Health care providers	• College of Oncology
	• National Hospital Council
	• Zorgnet Vlaanderen
	• Medical specialists and pathologists
Health care payers	• RIZIV/INAMI
	• Christian Sickness Fund
	• Socialist Sickness Fund
Legislation and regulation	• Representative of Federal Minister of Social Affairs and Public Health
	• FPS Public Health (SPF Santé Publique/FOD Volksgezondheid)
	• Centre Cancer/Kankercentrum
Registration	• Belgian Cancer Registry (BCR)
Scientific association	• Fund Rare Diseases and Orphan Drugs

7.3.3 SWOT matrix

In this matrix, the first row presents the strengths and weaknesses of the current organisation of care. The second row deals with the threats and opportunities that could arise from a new model of organisation of care, structured around reference centres. When conflicting points of views emerged (the same topic perceived as a threat for one stakeholder and as an opportunity for another), both points of view were reported under respective titles.

The responses have been organised around 4 themes:

- The legislative framework
- The organisation of care (diagnosis, treatment, follow up)
- The evaluation of the quality of care
- The patient centeredness

STRENGTHS **Legal framework** • Existing care programmes in oncology (basic/advanced/children) • Existing reference centres for rare diseases • Concept of reference centres foreseen by/described in the Hospital Act • The European Directive on patient's rights in cross-border healthcare (2011/24/EU) asks each Member State to designate Reference Centres, especially for rare diseases, in the context of the European Reference Networks **Diagnosis, Treatment and Follow Up** • MOC/COM: healthcare providers have an increased awareness of the importance of a multidisciplinary approach; additional reimbursement codes for specific situations (new case, new event, altered therapeutic strategy and yearly follow-up) • Second opinion/peer-review: two successful pilot projects in Belgium in sharing data for peer-review (pathology revision in rectum cancer and review of target volumes for radiotherapy) **Quality of care evaluation** • Ongoing accreditation process in many hospitals, but on a voluntary basis and without (financial) incentives • Cancer Registry (data and expertise) • Ongoing development of quality indicators in oncology **Patient centeredness** • Good and rapid access to care (everywhere)	**WEAKNESSES** **Legal framework** • No evaluation yet of the programmes of care in oncology (no minimal criteria, self declared expertise) and hence no consequences if care is suboptimal • Previous negative advise from the National Hospital Council regarding centres of reference (year 2005) • No legal rule to prevent specialists and hospitals from delivering treatment to every patient with (rare) cancer (even if they lack expertise) **Diagnosis, Treatment and Follow Up** • Dispersion of expertise in diagnosis and treatment • MOC/COM: high variability in frequency, types of cases discussed, involvement of specialists, time devoted to MOC/COM • Heterogeneity in expertise of pathology laboratories • Rare use of second opinion/peer-review in pathology (no digital equipment, reluctance of profession, cost involved, fear of peer-review, no reimbursement) • Few clinical practice guidelines to support practice **Quality of care evaluation** • Legal mission of the College of oncology, but not fulfilled so far (judge and being judged) • No systematic quality monitoring • No impact of positive/negative evaluation (incentives/disincentives) **Patient centeredness** • No information/identification of reference centres • No systematic referral mechanism

OPPORTUNITIES	**THREATS**
Legal framework • RD 21st March 2003 foresees specific RD for rare/complex cancers (no concrete realisation so far) • By order of the Minister of Health renewed consultation of the members of the National Hospital Council[q] with regard to the installation of reference centres	**Legal framework** • It lasts very long to publish a RD on reference centres in paediatric hemato-oncology • Care programmes and the recognition of centres will be transferred to the regions/communities in the 6th phase of the reform of the state. This may also delay the legislative work.
Diagnosis, Treatment and Follow-up • Improvement in quality of care • Confirmation of diagnosis (second opinions) • Increasing financing of MOC/COM (first consultation, follow-up, supplementary MOC/COM) • Development and interest in e-health technologies • Improved efficiency of the healthcare system	**Diagnosis, Treatment and Follow Up** • Dreaded loss of income for health providers who refer their patients • Extra costs related to double reading (e.g. time, additional analyses) • Need for new clinical pathways (who refers, when, and to whom ?)
Quality of care evaluation • Performed by independent experts/authorities, preferably not involved in the delivery of care (e.g. Cancer Centre, Cancer Registry)	**Quality of care evaluation** • No threat identified
Patient centeredness • More transparency of the healthcare system: better information to patients, GPs and external specialists (Orphanet, patients' associations websites)	**Patient centeredness** • Decreased accessibility of care: higher travel costs for patients and relatives

[q] Nationale Raad voor Ziekenhuisvoorzieningen (NRZV) / Conseil National des Etablissements Hospitaliers (CNEH).

7.3.4 *Synthesis of stakeholders' opinions, suggestions and concerns*

1. Is there an agreement on the organisation of care around reference centres for rare and/or complex cancers?

The concept of reference centres was thoroughly discussed. The majority of stakeholders expressed the absolute necessity to centralise expertise for rare and/or complex cancers in a small number of hospitals; only a minority was opposed.

Proponents of a new organisation model around reference centres are mainly found among patients' organisations, representatives of university hospitals, sickness funds, RIZIV/INAMI, and the scientific association "Fund Rare Diseases and Orphan Drugs".

Opponents are mainly found among representatives of non-university hospitals. But it has to be said that some of the opponents are actually in favour of the identification of reference centres for rare cancers, but they fear that the centralisation idea will be extended to all cancers requiring complex treatments (e.g. because they have already done quite some investments). In addition, most so-called opponents also admit the added value of a multidisciplinary management of rare cancer patients in reference centres, that can guarantee the expertise and required facilities, but they insist that also non-university hospitals will be eligible to become recognized as reference centre.

Legislation and regulation stakeholders (FOD/SPF, Cancer Centre, representative of the Minister) expressed no official opinion on this topic.

2. Why opting for reference centres for rare and/or complex cancers? What are the opportunities of this organisation of care?

Many stakeholders point as main pro argument the improved quality of care if care for patients with rare and/or complex cancers will be organised in centres with multidisciplinary expertise. First of all this will lead to a better diagnosis, as every reference centre should have a close collaboration with a reference laboratory in pathology. In addition, the definite confirmed diagnosis should be approved by a team of two or more (expert) pathologists, all taking responsibility for the final conclusion in the pathology report. This is considered essential for the correct diagnosis of rare cancers. The diagnostic confirmation should be used as starting point for the referral of patients with rare cancers to expert centres. According to some stakeholders, the actual network of pathology laboratories is fragmented and there are too many low-volume laboratories. As a result, there is a lot of heterogeneity in materials used by laboratories and in the additional tests performed, which leads to varying levels of quality.

After the diagnostic phase, patients will be offered a better quality of care in reference centres as the multidisciplinary team has expertise and can build up routine. In addition, patients seen in reference centres will have better access to complex and new targeted therapies and they will benefit from adequate surveillance of (adverse) treatment effects. They will thus face better outcomes at the end. Patients' organisations also emphasize the importance of being taken care not only by experienced physicians, but also by well-trained and skilled nursing and paramedical staff (e.g. psychosocial support).

Another argument in favour of reference centres is more transparency. At present, patients, GPs and relatives often do not know where to find sufficient expertise when diagnosed with a rare and/or complex cancer. If centres will be officially certified as a reference centre for a certain pathology, this information can be made readily available on official websites, in flyers (made available by GPs and hospital, sickness funds and others) etc. As there are currently no formal certified centres of expertise in Belgium, this information does not exist and is therefore not available to the patient or to their general practitioner. International examples of websites to inform patients and their caregivers already exist (e.g. Orphanet website). The identification of reference centres would thus lead to improved transparency of the location of high level care for patients and their caregivers (e.g. general practitioners and external specialists).

The organisation of care around reference centres can also help overcome the problem that at present there is no formal referral mechanism in the healthcare system that designates the provision of certain types of care to certain healthcare providers. At the moment there are no regulations for healthcare providers at which phase or in which situation they have to refer patients to someone who has more expertise. Patients can only thrust that they are taken care of by an experienced professional (team), but they have no means to check that.

Another important argument in favour of reference centres is an improved efficiency of the healthcare system, avoiding dilution of complex expertise and costly infrastructure (by concentrating human and technical resources and expertise, an optimal allocation of resources for a limited number of patients).

3. Why not opting for reference centres for rare and complex cancers? What are the threats of this organisation of care?

One of the consequences of a more centralised organisation of (rare and/or complex cancer) care is the fact that travel distances for patients and relatives become longer. However, a members' survey organised by one of the Belgian patients' organisation revealed that patients agree that quality of care is much more important than proximity. This view was shared by other stakeholders (e.g. medical specialists), who witnessed that patients are willing to travel long distances if they will be offered optimal care. On the other hand, longer travel distances imply higher costs for patients. Hence, reimbursement of travel costs and the provision of accommodation for close relatives should be considered when patients are referred to a reference centre far from home. Probably one of the best solutions for a good balance between quality and proximity is to opt – whenever possible– for a shared care model ("safe and effective services as locally as possible and not local services as effectively and safely as possible", NICE, Oncology for children, UK), as discussed in section 4 below.

Another concern expressed by the patients' representatives is that centralisation can potentially result in increased waiting times. This should be carefully monitored so that a sound equilibrium can be established between a very stringent/an efficient centralisation of care and accessibility of care.

During the meeting, one of the concerns with regard to centralisation of care raised by the healthcare professionals is the potential loss of financial revenues. The current financing mechanism of the Belgian health care system, characterized by a fee-for-service payment for most medical acts, does not encourage referral of patients. Referring patients to more specialised physicians in Reference Centres, implies a loss of financial resources, for themselves, but also for related services in the hospital. Some stakeholders representing medical specialists also fear a decreased ability to care for patients with rare conditions if specialists working in non-reference centres have to focus mainly on common situations.

4. How to organise the network between reference centres and peripheral centres? (and how to adapt clinical pathways?)

All stakeholders in favour of a new organisational model recommend the formation of networks between reference centres and peripheral centres. In this model, the reference centre is responsible for the diagnostic confirmation, the elaboration of the treatment plan and the complex parts of the treatment (for instance complex surgery or radiotherapy), whereas the peripheral centre would be responsible for the implementation of certain (or all) parts of the treatment plan. This type of network should be carefully tailored per rare and/or complex cancer type.

To facilitate a smooth transition of patients between Reference and peripheral centres and to keep the patient optimally informed, a 'liaison function' has to be installed. Such a care coordinator is essential for the follow-up of the referral process; it will guarantee patients that they will receive optimal care at the reference centre as well as at the peripheral centre and it will assure them an efficient information transfer. The care coordinator should not only be involved in the medical aspects of the care pathway, but also in the paramedical aspects. He/she should also be involved in networking with the family doctor and the domiciliary care facilities. Some stakeholders argue that the onco-coaches or specialized nurses in oncology who currently coordinate the oncology care could ideally accomplish this mission. At present, the onco-coaches are financed by the National Cancer Plan.

The number of reference centres certified for a certain rare and/or complex cancer should be based on the yearly incidence. If for certain pathologies or treatment modalities insufficient experience is present in Belgium, patients should be informed, the medical team should refer patients to European or international Reference Centres and the liaison person should facilitate the logistics of the referral.

The importance of identifying qualified medical staff

In order to avoid that patients with (rare) cancers are being diagnosed and/or treated by a medical staff that does not have sufficient skills and/or experience, it is suggested by one of the stakeholders to add 'addenda' to the specialists' RIZIV/INAMI registration number, which identify extra training and expertise in certain subspecialties (e.g. certain types of surgery). In order to guarantee that Belgian patients are no longer taken care of by self declared specialists (who actually lack the required training, skills and expertise), the reimbursement of certain procedures could be made conditional on the fact that they are performed by qualified specialists (i.e. who have the registration number addendum). Several stakeholders experience it as a flaw in the medical legislation that health care providers who do not have sufficient skills and/or experience cannot be legally or financially punished if they perform procedures for which they are not fully licensed. As long as the adagio "freedom of diagnosis and treatment" ranks first, patients with rare and complex cancers may still be cared for by non-experienced physicians in non-expert centres. For instance, patients with breast cancer can still be treated outside a breast cancer clinic, without any legal or financial sanction as long as gynaecologists are not obliged to refer these patients to breast cancer centres.

The importance of the multidisciplinary approach

It is felt by the majority of stakeholders that the instalment of multidisciplinary consultations (MOC/COM)[r] has improved the quality of cancer care in Belgium. Since then cancer pathways are developed and evaluated in a multidisciplinary setting. The increasing frequency of MOC meetings may illustrate the awareness of health care providers for a multidisciplinary approach. Nevertheless, there is still a high variability between centres, and between tumour types. For instance, rare cancer cases (bone and soft tissue sarcoma, malignant melanoma, thyroid cancer, urinary tract cancers and primary site unknown tumours, i.e. <60%) are significantly less frequently discussed during MOC meetings.[2] Some patients are less frequently discussed for other (debatable) reasons (e.g. elderly patients).[33]

With regard to the registry of the MOC/COM, some stakeholders suggest to add specific items related to rare tumours to the questionnaire sent to the BCR, such as the second reading of slides. In addition, pathologists should have the opportunity to access all data that permits independent interpretation of the pathology report, inclusive a second reading of the histochemically and immunohistochemically stained slides. The ideal pathology report should be accessible to all healthcare practitioners and should give the opportunity for access to data that permits independent interpretation by appropriate members of the healthcare team. Also, a well structured, automated pathology report would improve communication between pathologist, clinical specialist and the BCR.

Besides, a larger (than suggested by the law) panel of specialists, involved in the diagnosis and the treatment of rare cancer patients, should join the MOC discussions. This is actually already the case in the larger centres, where MOCs are organised by pathology.

In addition to the MOCs organised at the Reference Centre level, it is also recommended to install 'super MOCs', allowing experts from several reference centres to discuss more difficult cases. This will only be feasible if sufficient reimbursement and adequate logistics are provided.

5. What are the main obstacles for an organisation of care around reference centres?

A first obstacle or difficulty, which is very specific to the type of cancer, is the correct diagnosis as it is mainly based on pathological analysis of a tissue sample, often removed during a surgical intervention. Furthermore, it will be necessary to clearly describe and define per cancer type at what stage of the clinical pathway referral can be best performed. This should be defined in new clinical pathways.

[r] Since 2003, the multidisciplinary consultation (MOC/COM) has been legally defined and reimbursed. It should comprise at least four physicians coming from different specialties: a medical oncologist and/or a radiation oncologist and/or a surgeon with special competence in oncology.

Another issue raised is that based on the continuing advances in molecular biology more and more “common tumours” have rare subtypes. In addition, tumours situated in very different parts of the body can share the same molecular characteristics, and hence require a similar treatment strategy. In the future, care pathways will have to take these advancements into account.

Other issues that have to be considered when building networks between reference centres and peripheral centres, are linguistic and ideological differences between centres.

Also, one very important obstacle for the implementation of a new organisational model is the fact that there is no standard electronic patient filing system, which may hinder and delay the transfer of medical information between e.g. the reference centre and the peripheral centre. Setting up IT systems designed for data sharing with different healthcare facilities across the country will be essential. Another option for timely data exchange could be the set-up of a well secured web-based database holding patient records which could be accessed by healthcare practitioners across the country, as is for instance the case in Denmark. This would also save money as double diagnostic tests (medical imaging, laboratory results) can be avoided.

Finally, it will also be necessary to discuss in depth with medical specialists which type of rare cancer will benefit from a double reading of slides. Two pilot projects (Procare and a pilot project on radiotherapy and pathology revision) already illustrated the positive impact of a second opinion. New IT technologies such as electronic scans of the slices (sent by e-mail or made available on platforms for digital data exchange) could help reducing delays and removing the fear for potential loss of material when sent by regular mail. The double reading of slices will render improved diagnosis of certain types of cancer (an important example was France), but obviously, it has also financial implications induced by doubling work and extra investments for equipment. The implementation of double reading and peer reviewing should be performed with care (and some legislative enforcing help?) since e.g. the imaging (online) project was not successful at all. Only few radiologists were willing to participate in the study. Although the technological system was considered quite advanced, only 10-15 cases were entered.

6. How to evaluate the quality of care?

The College of Oncology is responsible for developing, assessing, implementing and disseminating good practice guidelines, and for developing quality indicators to assess clinical practice in oncology. The College is legally allowed to carry out field visits to validate implementation efforts and results. So far, the college has not taken this opportunity. The College of Oncology is composed of clinicians who are currently working in Belgian hospitals: they are both judge and can be judged, hence it is difficult for them to evaluate the quality of care delivered by themselves and by their colleagues. Some stakeholders report that quality surveillance and audits are essential when one wants to improve the quality of care. They should be performed by independent (auditing) specialists. In the Netherlands they already have quite some experience (and positive impact). Other structures were created that could contribute to the evaluation of care based on sets of quality indicators, especially the Cancer Registry, which has the required data, the know-how, to analyze quality indicators and to give feedbacks to practitioners and hospitals.

For some cancers (i.e. breast, testis, oesophagus, stomach, rectum) a set of quality indicators already exist but in the absence of a systematic quality monitoring system for care processes, there is no tool to distinguish centres with good quality from the others. Also, at present there is no impact at all of a potentially negative quality of care evaluation: there are no formal incentives to encourage hospitals to improve their quality of care and no formal disincentives to stop clinical activities (even) when (minimal) quality requirements are not met. Hospitals and health care providers should be encouraged to engage in quality projects (outcomes registry, feedback, action plan, new measurements).

All stakeholders emphasise the importance of the continuous evaluation of the quality of care delivered. Also the care provided in reference centres should be evaluated on a regular basis, so that “static and lifelong” designation/certification of centres which, once recognised, can no longer demonstrate outstanding outcomes, can be avoided. Reference centres should also have the obligation to register their patient volumes, their processes and outcomes, and can lose their recognition e.g. on the basis of demonstrated suboptimal quality of care or too low case load (insufficient expertise).

7. How to proceed next? What would be the legal basis to recognize reference centres?

At present there is a legal framework for the organisation of oncology care in Belgium. Since 2003, there is a care programme for basic oncological care and an oncology care programme (which should provide more advanced care). But again, these are based on criteria without formal control. Moreover, the recognition is based on self-declared responses, and not on an external evaluation. It is thus not possible to distinguish between centres with recognized expertise and self-declared ones.

In addition to these two general care programmes, a specialised care programme for breast cancer has been adopted in 2007, aiming at the concentration of breast cancer management in recognised breast cancer clinics. In 2013, 52 hospitals were certified for a specialised breast cancer programme. Again, the impact of this programme on the management of breast cancer women and the clinical outcomes is still unknown, as evaluation is lacking. But, what is even more important, the Royal Decree is not binding: no legal requirement prevents medical specialists working in hospitals without this recognition to treat breast cancer patients, nor are there financial (dis)incentives that would encourage patients to seek care in a recognised breast cancer clinic (if they have been informed about the existence of breast cancer clinics).

The Royal Decree of 21st March 2003 stipulates that a number of specialised care programmes have to be developed that focus on patients with cancers that need a complex multidisciplinary approach and/or extremely specialized expertise and/or that are very rare. A separate care programme for the organisation of paediatric cancer is planned to be published in the near future (after several years of negotiations). So far, no action has been taken in this field. Several stakeholders emphasise that this AR/KB is a good starting point for an improvement in the organisation of cancer care in Belgium. They suggest adding specific norms to the current norms of this AR/KB, with specific focus on the management of patients with rare cancers and cancers requiring complex care. However, the sixth phase of the federal reform will transfer the authority of setting norms entirely to the communities. Therefore, the recognition by means of a convention with RIZIV/INAMI may be a more pragmatic manner to recognise reference centres in the near future. In this way, uniform norms can be adopted for Belgium as a whole. A number of stakeholders recommend limiting the reimbursement of diagnosis and (certain parts of) rare cancer treatment to reference centres, which is actually already the case for a limited number of treatments (e.g. for instance dendritic cell therapy for high-grade gliomas or for malignant melanoma are given currently only in a limited number of centres).[s] If conventions are installed with NIHDI (RIZIV/INAMI), the candidate Reference Centres should reflect in advance whether this will be financially sustainable as conventions only pay on a fee-per-patient basis. Hence, if a centre does not obtain the number of patients described in the threshold, there is no payment at all for any of the patients seen in the centre. Also, it has to be realized that conventions often have a temporary perspective whereas arrangements described in an AR/KB are long-lasting. An in-depth evaluation and discussion with all concerned stakeholders will be necessary to explore the most beneficial way reference centres can be financially supported.

In article 14 of the Hospital Act, the legal framework for reference centres has already been provided. However, when asked by the Minister of Health to formulate an advice on the opportunity to organise cancer care differently in 2005, the National Hospital Council formulated a negative advice, because too many obstacles were identified to implement this article. Following multiple media and political reactions on the publication of the KCE report on quality indicators in the management of oesophageal cancer, the Ministry of Health has repeated its request for advice. This advice was expected for October 2013. However, nothing has been released so far.

[s] See recent AR/KB (December 2012, http://reflex.raadvst-consetat.be/reflex/pdf/Mbbs/2012/12/17/122940.pdf) .

8. How to proceed next? On which basis should reference centres be identified?

Due to the diversity of rare and/or complex cancers, stakeholders agree that hospitals should not be recognised or certified as reference centres for *all* rare/complex cancers. Yet, a hospital can be recognised as reference centre for more than one rare/complex cancer (e.g. reference centre for sarcomas, reference centre for head and neck cancers, reference centre for rare lymphomas).

Among the proponents of reference centres, the majority of stakeholders recognise the need to define a set of norms, which should be based as much as possible on scientific evidence. Some stakeholders would only consider university hospitals as reference centres whereas some others remark that the preface 'university' does not always imply quality. They prefer therefore to take into account other parameters such as quantitative criteria e.g. patient volume, volume of surgical interventions, number of COM/ MOC, number of referral COM/MOC, diagnostic confirmation (double reading of slices in pathology, or other diagnostic and staging tests), dedicated medical and paramedical staff, particular attention to patients information Other stakeholders opt for a recognition based on demonstrated results (better outcomes, better quality of care) rather than simply norms.

A very pragmatic proposition from one sickness fund to help identify the reference centres is to start from those centres which have already built a certain know-how and expertise, and then fully evaluate in the coming years those recognised centres based on criteria mentioned above. The Belgian Cancer Registry possesses the required data to perform such analysis, based on the last 10 years of national registration. The process of recognition should be transparent and this whole process, if publicly disclosed, would also improve the accountability and transparency of the system for the citizen/patient (e.g. reporting on the Orphanet website and on each reference centre website).

9. How to proceed next? Who are the main actors for a change?

All stakeholders have a role to play if a new organisation of care for patients with rare and complex cancers has to be installed:

- Regulators: identification of instruments able to introduce a change (regulation, accreditation, financing).
- Healthcare practitioners and medical associations can play a major role in identifying specific criteria to be fulfilled by reference centres (e.g. criteria defined by SONCOS in the Netherlands).
- Financing bodies (sickness funds and private insurance companies): in some other countries (e.g. the Netherlands, Germany, USA) insurance companies play a major role in the delivery of information to patients; for instance, they establish a list of hospitals where high-quality care will be delivered and (fully) reimbursed, with very short waiting times.
- Patients' associations: in the Netherlands, the Dutch Federation of Cancer Patient Organisation (NFK), grouping 24 associations, represents the interests of people who have cancer or have ever had. The Federation is heavily involved in cancer care policy.
- Scientific institutions: the Fund for rare disease can provide expertise with regard the recognition of centres.

In conclusion, all the ideas described above, should fit in a comprehensive change in the organisation of care for patients with rare cancers. It is expressed by several stakeholders that if only some aspects are taken care of, the impact of change may be very limited. If changes are made, they should be seen as vital links in a chain of change.

8 REFERENCE CENTRES IN ONCOLOGY: CONCRETE PROPOSITIONS

8.1 Introduction and objectives

An important task assigned to the KCE by the Minister was to propose new concepts for the organisation of care for adult patients with rare cancers and cancers that require complex care. Instead of limiting our report with the analysis of Belgian data to define rare cancers and the illustration of healthcare services for patients with rare/complex cancers implemented in other countries, we have decided to follow a more innovative and ambitious approach. For this specific purpose, several multidisciplinary working groups were constituted to propose concrete recommendations for the organisation of care for patients with rare/complex cancers, adapted to the Belgian context.

8.2 Methodology

8.2.1 Initiation of the project

Strategies to improve the quality of care for rare/complex cancers
Reduce the delay of **diagnosis** and decrease the number of misdiagnoses
Ensure care is delivered according to EBM standards
Ensure complex treatments are performed by experienced professionals
Stimulate the development of multidisciplinary environments
Ensure access to innovative treatments **(in Belgium or abroad)**
Identify and **concentrate** expertise
Create links between experts and between centres
Create processes for **referral**
... ?

In **June and July 2013**, we launched a first invitation to medical experts involved in the management of rare/complex cancer patients to collaborate. The objectives of the study were presented, as in the previous scheme, and suggestions were asked for the last empty box.

Due to the summer season, first meetings were held at several occasions and locations. These meetings aimed to evaluate the acceptability and the feasibility of our approach, and to assess the medical experts' interest in collaboration in this project. In addition, we intended to delineate a list of cancer groups – based on rarity or complexity of the management – for which concrete proposals for an improved organisation of care could be elaborated.

For this purpose the following definitions for rarity and complexity were applied:

A cancer is considered rare when it affects less than 6 new adult patients/100 000 adult inhabitants/year (based on the RARECARE categorisation).

A cancer requiring complex care is defined as

- a cancer on a very specific and extremely difficult to reach anatomic localisation (for instance a brain tumour or an ocular tumour),
- a cancer occurring during a specific condition (for instance a cancer occurring during pregnancy),
- a cancer requiring a high level of expertise, because of its diagnosis and/or treatment (for instance soft tissue sarcoma, oesophageal cancer),
- a cancer requiring very high-tech or costly technical infrastructure (for instance HIPEC treatment for tumours of the peritoneum).

Wherever in the text the term “rare/complex cancer/tumour” is used, we refer to these definitions.

Based on these criteria, the epidemiological (incidence) data for Belgium, the experience from other European countries, the feasibility within a very limited time frame and the availability of medical experts, resulted in the following list of rare and/or complex cancer types for which proposals for an improved organisation of care were further elaborated:

Table 8 – List of rare and /or complex cancer types for which proposals were elaborated

Rare haematological cancers
Rare cancers of the female genital system
Cancers of the head and neck
Cancers of the oesophagus
Cancers of the pancreas and hepatobiliary tract
Malignant skin tumours
Cancers of the Central Nervous System
Rare cancers of the endocrine organs (thyroid)
Cancers of male genital system (testis, penis)
Neuroendocrine tumours (NETS)
Malignant mesotheliomas
Cancers occurring during pregnancy
Cancers of the Peritoneum
Familial adenomatous polyposis (colorectal cancer)

The proposals were formulated by **14 multidisciplinary working groups**, which involved **220 clinical experts** from about 30 different university and non-university hospitals, from different ideological backgrounds, from Flanders, Brussels and Wallonia. In the future, similar work should be done for other rare and complex cancer types (e.g. cancer of the thymus, renal cancer, soft tissue and bone sarcomas, complex lung surgery...) that could not be covered within the frame of the present KCE report due to time constraints.

8.2.2 Working process

The trajectory of the multidisciplinary working groups involved three main steps:

Step 1 - Installing a multidisciplinary (medical oncology, surgery, pathology, radiotherapy, medical imaging, nuclear medicine...) working group, with clinical experts and pathologists with specific interest, clinical experience and/or subspecialty training in rare or complex cancer concerned, from different hospitals (university and non-university), from different ideological backgrounds and from across the country.

Although the coordinators of the groups were asked to involve university as well as non-university affiliated experts, the majority of participants were affiliated to university hospitals. Apparently it was not evident for some groups to get non-university affiliated colleagues involved (e.g. lack of time, lack of expertise, lack of interest).

Once the group was composed, its members designated the working group coordinator. The complete composition of the working groups is reported in the proposals, which are added to the scientific report as appendix and can be found on the KCE website.

Step 2 - Identifying the cancer subtypes and the phases of the clinical pathway that require a management in Reference Centres. Whenever possible, the RARECARE definition and typology (layer 1 and layer 2) were applied. For some working groups (e.g. cancers occurring during pregnancy, familial adenomatous polyposis), it turned out difficult to follow this methodology. The coordinators provided a precise description of the included cases.

Step 3 - Defining detailed eligibility criteria for a Reference Centre to be certified as such. Each group was asked to develop a detailed proposal for an improved organisation of care for the cancer type it was assigned. They were explicitly asked to start from the patient's perspective. An important message shared with all coordinators was that they should avoid any monopoly by university hospitals. In addition, they should not define the number of hospitals to be recognised as Reference Centres.

The starting point was the Royal Decree of 21st March 2003 that defines criteria for oncology care programmes (i.e. criteria to offer more advanced diagnostic options as well as various therapeutic possibilities). The working groups were asked to define criteria supplementary to those stipulated in the Royal Decree on oncology care. The supplementary criteria should ensure that recognised Reference Centres truly apply a multidisciplinary approach and acquire and maintain high expertise on the rare cancers they are recognised for.

To support the working groups, eligibility criteria for (rare or complex cancers) Reference Centres applied in other countries (e.g. SONCOS criteria, BCBSA criteria, OECI criteria, NHS contracts for UK) were provided. It was mentioned clearly that those documents could be used as a starting point for discussions and that the content not necessarily corresponded to the views of the KCE team. The working groups worked autonomously but reported the progress of their activities on a regular basis to the KCE team.

A comprehensive template was sent to all coordinators to structure the reflections and to ensure the homogeneity of the proposals. The template comprised the following main topics:

Short description of this cancer type (epidemiology, aggressiveness, prognosis, symptoms, ...)

For which phase of the clinical pathway are Reference Centres required for patients with this cancer? (diagnosis, treatment, follow-up, ...)

Ideally, which model has to be applied for the organisation of care?

Model 1: Reference Centres exclusively (from diagnosis to follow-up). Once a patient is suspected of the cancer, he/she should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.

Model 2: Shared care between Reference Centres and local hospitals. For example, the first contact is taken with a Reference Centre (diagnostic step and MOC), then the patient can be referred back to the referring hospital (for treatment, palliative care, follow-up).

Model 3: Alternative, proposed by the working group.

Detailed list of specific criteria (in addition to those required by the oncology care programme) that have to be fulfilled by a hospital that would like to be recognized as Reference Centre: human resources and dedicated team, multidisciplinary management, required facilities and equipment, patient centred care, minimal volume of patients, quality assurance research and other scientific activities, teaching and dissemination.

The actual work of the 14 different multidisciplinary working groups was performed from September to December 2013. Each working group adopted its own work methodology (e.g. face to face discussions, teleconference, e-mail discussions) and formulated proposals according to its own insights and methods. Draft versions of the proposals were regularly reviewed by the KCE team. During four feedback meetings with all working group coordinators and the KCE team, practical aspects, difficulties and controversial issues were discussed in plenum.

8.3 Policy recommendations for a more effective organisation of rare/complex cancer care for adult patients

These recommendations are based on the findings from the literature review, the views of the stakeholders (see colophon) and the detailed proposals formulated by the multidisciplinary cancer working groups and the panel of pathologists. They were carefully pondered by KCE experts against the backdrop of the current organisation of care for rare and complex cancers in our country.

8.3.1 Core recommendation: Set-up of shared care networks around Reference Centres

To improve the quality of care and to decrease the dispersion of expertise and experience, Reference Centres (RC) with multidisciplinary teams of recognized clinical and technical expertise in specific rare/complex cancers should be established and certified.

The formation of networks or functional relationships between Reference Centres and Peripheral Centres ("shared care model") will allow a delivery of care combining expertise and proximity.

In Peripheral Centres only less complex well-described parts of the treatment can take place, and they should be performed under supervision of the Reference Centre. A Peripheral Centre should get guidelines about when they have to confer with a Reference Centre about a rare/complex cancer patient.

Note: *A Reference Centre is not to be understood as necessarily situated in a university hospital. Likewise, the term "peripheral centre" is used to designate a hospital/campus that is not certified as a Reference Centre for the cancer type concerned. It does not entail any qualitative or geographical connotation, nor does it refer to a non-university status.*

What can patients with rare/complex cancers expect from shared care networks organised around Reference Centres?

The most fundamental benefit patients can expect from **shared care networks organised around Reference Centres** is a **better chance of survival, lower relapse rates and lower complication rates**.

More specifically, patients with a rare/complex cancer can easily identify Reference Centres by themselves. They will be referred by their general practitioner or their specialist. In the Reference Centre the first diagnosis and staging will be further elaborated by expert specialists (e.g. double reading of slices, access to molecular biology, additional/high imaging technology if needed). Patients can expect to benefit from a more standardised diagnostic and therapeutic approach and will be ensured that their case will be discussed by a multidisciplinary group including the appropriate experts in diagnostics as well as therapy. As patients' management will be in the hands of an experienced multidisciplinary team working in a Reference Centre with sufficient case load, short-term and long term outcomes will be better. In addition, they will have a direct access to more advanced or innovative treatments; they will be treated by experienced and skilled healthcare providers (including well-trained and skilled nursing and paramedical staff) and can be recruited in clinical trials if applicable. A direct link with patients' associations will offer them psychological support and help. Finally, the structured collaboration between the Reference Centre and the Peripheral Centre and the continuous quality assurance of the care processes, will have a positive impact on the quality of care delivered in the Reference Centre as well as the peripheral centre. Furthermore, the shared care model will offer patients the combination of high quality care and proximity.

Under 6.1 we will detail the recommendations with regard to the Reference Centres and under 6.2 the shared care network is further elaborated. Under 6.3 the recommendations with regard to second opinion in pathology are depicted and finally under 6.4 the support to patients and relatives is described.

8.3.1.1 *Reference Centres: expertise, multidisciplinarity and accessibility*

Recommendation 1

To become recognised as Reference Centre hospitals should meet strict criteria in addition to those specified in the oncology care programme legislation.

These criteria should ensure that recognised Reference Centres truly apply a multidisciplinary approach and have sufficient expertise in the rare cancers they are recognised for.

To become recognised as Reference Centre for a certain cancer (group), hospitals should not only fulfil the minimal requirements for the oncology care programme, they should also meet the special requirements for diagnosis and treatment of rare/complex cancers. For 14 of the rare and complex cancers listed in Table 8, these criteria have been very thoroughly elaborated (see the proposals from the working groups - KCE website).

It is evident that Reference Centres should receive sufficient financial support so that they can invest in extra (para)medical expertise and expensive infrastructure. Financing through agreements with RIZIV - INAMI ("conventies/conventions") is a proven formula that could well meet this specific context.

8.3.1.2 *Dedicated teams and adequate facilities*

Recommendation 2

Reference Centres need more specifically skilled medical and paramedical staffing than required by the programmes in oncology. In addition, they should be equipped in function of the rare/complex cancer they are certified for.

Reference Centres should have the resources to provide high-quality, continuous, comprehensive care delivered by a multidisciplinary team with a special interest and expertise in the cancer concerned. Not only medical experts have to be involved, but also a highly skilled (para) medical staff (e.g. clinical nurse specialists, dieticians and nutritionists, speech therapists, dentists, physiotherapists, psycho-oncologists, social workers).

The organisation and financing of the care should ensure that patients with rare/complex cancers are systematically directed to these teams which have the required training, expertise, skills and infrastructure. **The systematic referral** can be accomplished by limiting the reimbursement of certain procedures to specifically qualified specialists and recognized Reference Centres.

A patient with a rare/complex cancer should find all expertise (multidisciplinary team and necessary technical equipment) on 1 campus. Concomitant treatments (e.g. chemoradiotherapy) should definitely be offered on the same hospital site. Subsequent follow-up treatment can be offered in a peripheral hospital, under the supervision of the reference centre, provided the required skills are available and of sufficient quality (see recommendations 9 and 10).

Also from an economical perspective, concentrating very expensive treatments and costly equipment in a limited number of centres, is more cost-effective.

A transition period could facilitate the needed structural reforms, but should be limited in time.

For detailed descriptions, the reader is referred to the 14 proposals, where the specific requirements are described in more detail on the KCE website.

8.3.1.3 *Multidisciplinary oncological team meeting (COM/MOC)*

Recommendation 3

Specialised multidisciplinary oncological consults (COM/MOC) should ensure optimal management of patients with rare/complex cancers. The panel should involve medical and paramedical experts with a specific expertise in the management of patients with the cancer in question (diagnostic and therapeutic strategies, supportive care). The composition of the panel of experts will vary according to the cancer types discussed and the phase in the disease.

Rare cancer cases are significantly less frequently discussed during MOC/COM meetings (e.g. bone and soft tissue sarcoma, malignant melanoma, thyroid cancer and urinary tract cancers <60%).[30] Hence, extra efforts should be made by the Reference Centres to discuss each rare and complex cancer case with an appropriate multidisciplinary panel.

As proposed by many of the working groups, rare cancers that were already discussed during a MOC/COM meeting in the peripheral hospital should benefit from a second specialised MOC/COM at the Reference Centre. The current regulations already provide for the reimbursement of these second-opinion MOC/COMs under certain conditions, which may need a thorough re-evaluation.

With regard to the registration of the MOC/COM, specific items related to rare tumours, such as the second reading of slides, should be added to the standard questionnaire sent to the BCR.

In addition to the MOC/COMs organised at the Reference Centre, it is recommended to install 'super MOCs/COMs' at a higher level, allowing experts from several (also international) Reference Centres to discuss more difficult cases. Tele-MOC facilities, including audiovisual facilities, will support and encourage discussions between specialists from different institutions.

As the current remuneration modalities for the MOC/COMs might not be appropriate for the specialised MOC/COM, the 'super MOCs/COMs' and the participation of medical experts from Reference Centres attending MOCs/COMs at peripheral centres - either in person or via web conference – a reform or extension of the system should be considered.

This issue is further elaborated in each of the 14 concrete proposals.

8.3.1.4 *Patient-centred care*

Recommendation 4

Reference Centres have to ensure that care is based on the patients' needs and values. In order to guarantee that patients are actively involved in the clinical pathway they are offered, a liaison coordinator should be appointed.

Over the past two decades, patient-centred care has been recognised internationally as a dimension of high-quality health care. In 2001, the US Institute of Medicine (IOM) defined patient-centred care as 'care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patients' values guide all clinical decisions'. Patient-centred care implies that an effective and time limited care pathway is planned and specific support services are offered to the patient (identification of a care coordinator, link with patients' associations, specific website for patients / professionals...). In case of unusual, complicated ethical problems and end-of-life ethical issues, the ethics committee should be consulted.

The MDT team of the Reference Centre designates for **each patient a practitioner-in-charge** and its substitute, who acts on behalf of the MDT team. The practitioner-in-charge and its substitute are documented in the (digital) medical file and are known to the patient and his/her relatives. The practitioner-in-charge and its substitute act in close collaboration with the liaison-coordinator.

Following the COM/MOC, the general practitioner (GP) has to be informed of the diagnosis and the therapeutic plan.

In order to ensure that each patient is actively involved in the clinical pathway s/he is offered, a liaison coordinator should be appointed. This person will play an important role in the transmission of information (e.g. about the diagnostic and therapeutic timelines) to the patient, his/her relatives and GP, and in the coordination of the different steps in the clinical pathway (e.g. which part of the pathway is performed in the reference centre and which part in the peripheral centre).

8.3.1.5 Minimum volume of patients

Recommendation 5

In order to halt the dispersion of care and to increase concentration of resources and expertise in rare and complex cancer care, it is recommended to impose minimum case loads for Reference Centres and medical specialists. These norms should be based on Belgian incidence data and international guidelines and should allow for a run-in period.

Within a reasonable time frame it should be realised that every patient with a suspicion of rare/complex cancer is referred to a Reference Centre in the early diagnostic phase.

The "volume-outcome relationship" has been demonstrated for numerous types of surgical and medical treatments (e.g. oesophagectomy, pancreatectomy, management of patients with testicular cancer). A smaller body of evidence has identified a number of specific structural characteristics or care processes associated with better patient outcomes. Volume may be a determinant by itself and/or may be associated with better perioperative care, including well-performed diagnostics (patient selection), pre-operative discussion of each patient in a multidisciplinary team, adequate perioperative care in the surgical department and in the intensive care unit with adequate numbers of skilled specialists and experienced nurses, and an infrastructure able to adequately deal with complications.

Reference Centres have to treat a sufficient volume of patients with rare/complex cancers to increase experience and expertise and to maintain this high level of expertise. This requirement is advocated by many stakeholders, convinced by the evidence from research.

Moreover, insofar as Reference Centres have a duty to monitor and report their performance and outcomes (see recommendation 6), among others by means of quality indicators, a minimum number of cases is needed in order to get meaningful and trustworthy results. From this perspective, the minimum volume requirement is an unescapable statistical dictate.

The corrolarium is that, on the one hand, the number of Reference Centres per type of cancer is kept (very) low and, on the other hand, all other hospitals are forced to stop treating rare/complex cancers.

Again, foreseeing a transition period will facilitate the needed structural reforms, but should be limited in time.

8.3.1.6 Quality Assurance

Recommendation 6

Reference Centres should only be certified if they meet specific requirements regarding expertise, experience and infrastructure. The quality of care provided in Reference Centres should be evaluated on a regular basis, so that "static and lifelong" certification of centres which, once recognised, can no longer demonstrate outstanding outcomes, can be avoided.

The quality of care delivered by Reference Centres has to be monitored on a continuous basis. These centres should participate in the relevant external quality assurance initiatives, which could both encompass regional or national quality systems and international auditing, benchmarking or accreditation for the specific cancer concerned. The principles of such an integrated quality assurance approach have been developped in KCE report 152 (2011). More specifically:

- For each patient, complete and valid information about the diagnosis, the cancer stage, the diagnostic procedures and the planned/given treatment should be sent to the Belgian Cancer Registry. This is part of the existing reporting obligation, applicable to all centres with an oncology programme. For each rare/complex cancer it should be evaluated which variables of specific interest should be added;
- Quality indicators (structure, process, outcome) should be developed and prospectively recorded. These indicators should entail both transversal dimensions, relevant for all cancer types (discussion in a COM/MOC, quality of the staging, short- and long-term survival, complication rate, re-entry surgery, patient satisfaction,…) and (a limited number of) more specific aspects, linked to the recommended care processes and specific outcome dimensions of a particular cancer type;
- The results should be pooled and analysed by an independent body, and standardised feedback reports should be sent to the individual centres, allowing them to benchmark their performance with their peers; this should preferably be organised in an international context, given the small number of cases and Reference Centres per country.

The objectives, content and modalities of this monitoring and feedback should be defined in close collaboration with the professionals involved in the day to day care, but the system should be set up and run by an external, dedicated team with expertise in data mangement and quality assurance.

In addition to the monitoring and feedback described above, it is recommended to organize periodic auditing or accreditation visits, again preferably in an international context.

Public disclosure of the results of the monitoring, the audits and the accreditation reports will increase the striving for excellence and should be envisaged once the data are available.

8.3.1.7 Scientific and educational activities

Recommendation 7

Reference Centres should be actively involved in clinical research to stay on the cutting edge of their field. In order to disseminate their medical expertise, they should also be implicated in continued education of health care professionals.

As the incidence of rare cancer is low by definition, experts working in a Reference Centre should participate in clinical trials in which rare cancer patients can be recruited (including local, national and international observational, translational and interventional studies of any phase). Medical experts working in Reference Centres should also be involved in the development of clinical practice guidelines. Reference Centres should also have a structural link with a tumour bank.

Reference Centres should disseminate their medical advances via publications in peer-reviewed journals, through professional training and communication towards the general public.

8.3.1.8 Networking at the European and international level

Recommendation 8

Healthcare professionals from Belgian Reference Centres should collaborate actively with colleagues from international Reference Centres. In case of (ultra)-rare cancers and highly complex procedures for which there is insufficient expertise in Belgium, referral partnerships should be set up.

The number of Reference Centres certified for a certain rare and/or complex cancer should be based on the yearly incidence. If for certain pathologies or treatment modalities insufficient experience/expertise is present in Belgium, patients should be informed, the medical team should refer and the liaison person should facilitate the logistics of the referral. It is recommended to establish criteria for the referral of patients from Belgian Reference Centres to European Reference Centres.

In addition, through international networking Belgian Reference Centres will not only increase their expertise but also their research potential, both on fundamental, translational and clinical research, including the participation in clinical trials.

8.3.2 A shared care model

8.3.2.1 Networking between Reference Centres and peripheral services for the delivery of care

Recommendation 9

The formation of networks or functional relationships between Reference Centres and peripheral centres that allow a delivery of care combining expertise and proximity (shared care model) is highly recommended.

Service Level Agreements (SLA) between the physicians and centres involved, have to address patient referral/back referral and patient follow-up.

To facilitate the transition of patients between Reference and peripheral centres, a 'liaison coordinator' has to be appointed.

In this model, the Reference Centre is responsible for the diagnostic confirmation, the elaboration of the treatment plan and the complex parts of the treatment (for instance complex surgery or radiotherapy), whereas the peripheral centre is responsible for the implementation of the other aspects of the care plan, in particular the less complex elements of the treatment or the follow-up.

This type of network or relationship should be tailored per cancer type. The majority of the working groups have advocated a shared care model rather than the concentration of the whole care pathway in the Reference Centre.

Each patient with a rare/complex cancer should be discussed during a multidisciplinary meeting in the Reference Centre, as first intent or as second opinion before any therapeutic intervention. Also in cases of relapse or recurrence, the patient should be discussed again during a multidisciplinary meeting in the Reference Centre.

Service Level Agreements (SLA) between the centres involved, addressing patient referral/back referral and patient follow-up are an essential element of the shared care network. These arrangements should entail (among others) the sharing or at least exchange of (electronic) medical records, information duty in both directions (on the medical, paramedical social and logistics level, e.g. smooth transportation process) and formal agreements on common care protocols. This should avoid undue delays and duplicate investigations.

To facilitate a smooth transition of patients between Reference and peripheral centres and to keep the patient optimally informed, a **'liaison coordinator'** has to be appointed in the Reference Centre. He/she should assure that patients receive optimal care at the Reference Centre as well as at the peripheral centre and will assure an efficient information transfer. The care coordinator should not only be involved in the medical aspects of the care pathway, but also in the paramedical aspects. He/she should also be involved in networking with the family doctor and the domiciliary care facilities.

The onco-coaches or specialised nurses in oncology, who are currently financed by the National Cancer Plan to coordinate the oncology care, can accomplish this mission. In some settings, social workers actively assist in discharge-planning activities, such as taking arrangements for home-care services or for the transfer to other healthcare settings.

8.3.2.2 Networking between Reference Centres and peripheral services for follow-up and rehabilitation

Recommendation 10

The networks and functional relationships between Reference Centres and peripheral centres should ensure continuity and coherence in the follow-up and rehabilitation of the patient after the specialised treatment.

The follow-up and rehabilitation of the patients after their specialised cancer treatment should pursue different objectives, including optimal physical, social and psychological functioning. Rehabilitation requires an interdisciplinary team approach because of the variety of potential problems and impairments induced by the illness process and the treatment.

According to the needs of the patients, the following specialists can be involved: care coordinator, physiotherapists, social workers, psychologists, occupational therapists, speech therapists, dieticians. Other professionals can also have an added value such as dentists, orthotists and prosthetists. In addition, rehabilitation programmes can benefit from consultative relationships with other care-providing organisations (e.g. home healthcare agencies, community services).

For detailed descriptions, the reader is referred to the 14 proposals, where the specific requirements are described in more detail (see appendix on the KCE website).

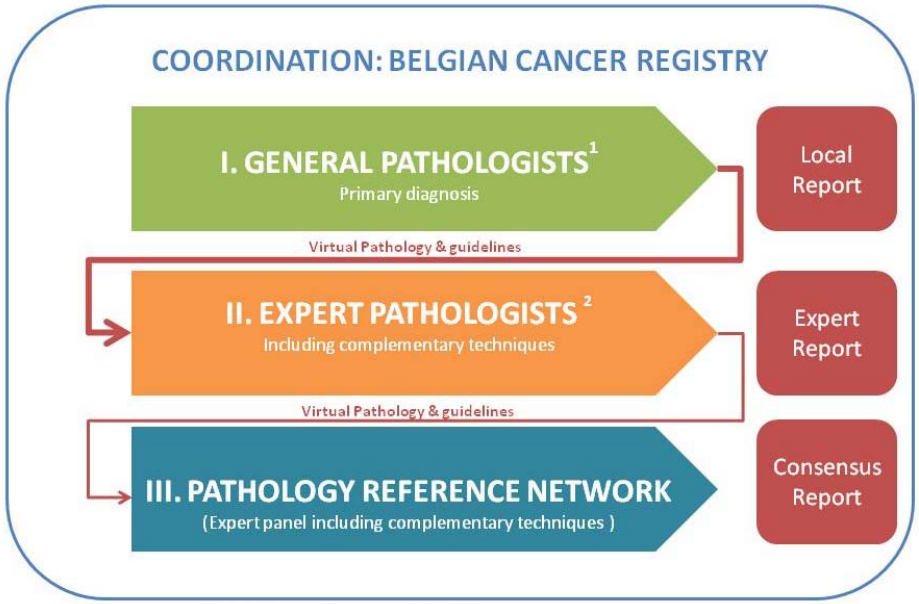
8.3.3 Second opinion in pathology

Similarly to the role played by the Centres for Human Genetics in the management of rare diseases, the Pathology labs have to play a key role in the management of patients with rare cancers. The panel of pathologists with expertise in rare cancer diagnosis consulted in the course of this study suggested a number of proposals for an improved diagnostic process of rare cancers[t]. Their proposals were unanimously accepted by the Consilium Pathologicum Belgicum, by the Commission for Anatomic Pathology, by the Belgian Society of Pathology (BWP) and by the GBS/VBS (Groupe des Unions Professionnelles Belges de Médecins Spécialistes/Verbond der Belgische Beroepsverenigingen van Geneesheren-Specialisten - Pathology).

Recommendation 11

A 'three-step' model of diagnostic confirmation of pathology findings is recommended for rare cancers (Figure 8). This protocol should be implemented as recommendation of good practice in licensed pathology laboratories.

Figure 8 – A 'three-step' model of diagnostic confirmation for rare cancers



(1) General pathologists belonging to a licensed pathology laboratory
(2) Expert pathologists recognised by the ISP/WIV

t P. Vermeulen, C. Colpaert, C. Cuvelier, P. Demetter, A. Mourin, P. Goddeeris, M. Petein, P. Delvenne, W. Waelput, R. Croes, R. Sciot, I. Salmon, T. Tousseyn, R. Achten, E. Mutijima, K. Cokelaere.

8.3.3.1 Definitions

An **expert pathologist** is a pathologist who provides a 'second opinion' on pathology specimens from rare cancer cases. This diagnostic confirmation has to be incorporated in the initial pathology report as "expert report" within acceptable time limits. The expert pathologist works in consultation with other national and/or international expert pathologists in a 'pathology reference network' where difficult cases are discussed and a consensus diagnosis is reached.

A **pathology reference network** represents a panel of national and/or international expert pathologists, who will assure the second opinion of difficult cases, for a given group of rare tumours leading to a consensus report.

8.3.3.2 Practical organisation

Expert selection

Similarly to recognition process of laboratories, pathologists should apply for recognition as an expert pathologist with advice from the Commission for Pathology (ISP/WIV). To this purpose a Working Group 'quality assurance of second opinion' should be installed within the Commission.

Selection criteria will be based on 'recognition by peers', activity in relation to rare cancers (number of cases seen, taking part in multidisciplinary oncology meetings (MOC/COM), considerable daily practice in the area of expertise), scientific visibility, involvement in research and publications. Moreover, the expert pathologist has to have easy access to the necessary ancillary techniques to obtain accurate diagnosis and prognostic report on the cancers relevant to his/her area of expertise.

Pathology reference networks' composition

The pathology reference networks should be composed of a minimum number of both academic and non-academic, national and/or international pathologists. The pathology reference networks are coordinated by a responsible pathologist elected for a term of 3 years. Timing of meetings is subject to specific needs. In order to minimise delays in answering time the use of digital pathology should be introduced.

The pathology reference networks have also:

- to promote research on these rare cancers through multicentre research studies, both at a national and international level,
- to contribute to the epidemiologic surveillance of these cancers by establishing a database for collection of relevant data, in collaboration with the Belgian Cancer Registry,
- to participate in the formulation of national recommendations for good practice, drawing on European or international guidelines.

In view of its relevance in the registration of all cancer cases, including rare cancers, the Belgian Cancer Registry would be the evident choice to coordinate this model of diagnostic confirmation of pathology data.

Daily practice second opinion organization

According to multidisciplinary oncological consultations (MOC/C0M) a demand for pathological diagnostic confirmation in rare cancer cases should be addressed by the general pathologist to an expert pathologist previously defined. This expert report should be delivered in a timely manner (e.g. one week), in order to minimise any delay in treatment and has to be integrated in the initial report by the general pathologist providing a clear unique diagnosis to the clinicians. In case of discordance or for more complex cases, the expert decides to refer to the pathology reference network in order to obtain a consensus diagnosis in a timely manner.

8.3.3.3 Quality Assurance

The pathology reference networks should draft an annual activity report. This report should include (non exhaustive listing) the number of cases discussed in the panel, number of cases seen in 'second opinion' by individual expert pathologists, concordance and discordance levels, ancillary techniques used by expert pathologists. This report should be communicated to the Commission for Pathology. The ISP/WIV presents an annual composite report on the entirety of 'second opinion' activities, in accordance with the national external evaluation programme.

8.3.3.4 *Virtual Pathology*

The vast advancements in telecommunications and converting medical information to a digital format have increased the number of medical applications including virtual pathology. In the last few years, telepathology has benefited from the progress in the technology of image digitalization and transmission through the world web.

Virtual pathology is a rapidly evolving niche in the world of pathology and is likely to increase in popularity as technology improves. Virtual pathology facilitates rapid, efficient communication between subspecialty pathologists and generalist pathologists. This approach allows 2nd opinion on challenging cases with fine-tuning of diagnostic interpretation and has many advantages. Indeed, virtual microscopy for 2nd opinion avoids mailing costs and loss of slides. In addition, the patients will benefit from a faster diagnosis via a secure web site. Consequently, faster patient diagnosis and treatment may decrease healthcare costs.

Furthermore, an extension to the existing 'Belgian virtual tumour bank' (biobanking) could be envisioned by the possibility of digital archiving of rare cancer cases.

8.3.3.5 *Financial aspects*

There is an evident cost to these 'second opinions': Besides logistics (transfer of slides, registration, reporting) there is an important investment in 'time and energy' of expert pathologists. No reimbursement for diagnostic confirmation of pathology data is currently provided. When considering the financial aspects of diagnostic confirmation of pathology data in rare cancers however, one should take into account other, less readily quantifiable costs. The impact on public health, patients, institutions and society of incorrect pathology diagnoses is crystal clear. A well-organised model for 'second opinions' will certainly lead to budget savings by avoiding unnecessary treatments (not to mention possible litigation costs of mistreatment).

Expert pathologists should receive a 'consultation fee' for the second opinion in the context of this programme. Coordination, secretariat and other missions of pathology reference networks could be funded through a NIHDI convention specific to this purpose.

Through the work of the Belgian Cancer Registry, in concert with many stakeholders, a very adequate estimate regarding the numbers of rare cancers can be made. These constitute only a fraction of daily pathology practice. The expected budget for these 'second opinions' would thus be very predictable and stable.

The diagnosis of these cancer cases, by their rare and complex nature, usually necessitates the extensive use of relevant ancillary techniques (e.g. immunohistochemistry, molecular biology), essential to provide a 'state of the art' reporting (fine-tuning of diagnosis, standard reporting, prognostication). It would therefore be reasonable to consider upscaling the current limit on reimbursement of these techniques.

In view of the many potential benefits of virtual pathology (especially time-wise), it could be sound financial management to fund the development of virtual pathology in Belgium, included use of digital slide-scanners, according to the existing project such as Belgian Virtual Tumour bank-Biobanking and Biomolecular Resources Research Infrastructure - Biobanking.

Finally, to manage the additional costs in general pathology labs (e.g. sending cases for double reading, registration of discordances) to be expected from this model of 'second opinion', a 'lump budget' per patient can be considered.

8.3.4 *Information and communication*

Recommendation 12

The setup of a national portal website which provides up-to-date information on rare cancers and Reference Centres for various users (patients, healthcare professionals, researchers, general public) and links to validated sources of information (including Orphanet) is recommended.

Disease-specific websites about patients' associations, networks of reference, registries or specific activities on cancers are very important sources of information.

The Rare Diseases Organisation Belgium (RaDiOrg.be), a coordinating alliance of 80 patients' organisations, is the official representative of Eurordis in Belgium. RaDiOrg.be created a web site to encourage the dissemination of information on rare diseases in Belgium. It provides a direct link to Orphanet, the European Portal for rare diseases and orphan drugs. Orphanet operates through a network of partner teams in different countries; these teams are responsible for collecting information on expert services and research on rare diseases. A specific page of this portal is devoted to the identification of Centres for expertise and networks in the management of rare cancers.

The setup of a national portal website which provides information on rare diseases (including rare cancers) was already suggested in the recommendations and proposed measures for a Belgian Plan for Rare Diseases[5]. The KCE subscribes this recommendation.

9 CONCLUSIONS

It is no longer practicable, efficient or ethical that every hospital and every practitioner continues to offer care for every rare/complex cancer. If one wants to improve the quality of rare/complex cancer care, the only option is to concentrate expertise and sophisticated infrastructure in Reference Centres, which have to comply with strict criteria to be certified as such. Moreover, European directives urge Member States to identify Reference Centres and to create networks with other Reference Centres throughout Europe. To ensure consistent quality of care, continuous quality assurance (e.g. through audits and accreditations) and regular re-certifications are essential. Furthermore, the formation of networks or functional relationships between Reference Centres and peripheral centres (shared care model) will allow a delivery of care combining expertise and proximity.

In order to prepare the path towards Reference Centres for rare and complex cancers in Belgium, 14 multidisciplinary working groups, involving as many as 220 clinical experts from 30 different university and non-university hospitals, from all regions of the country developed a series of concrete proposals for an improved organisation of care for 14 different rare or complex cancer types. In addition, a panel of pathologists with expertise in rare cancer diagnosis formulated concrete suggestions for an improved diagnosis of rare cancers.

The next step is the translation of the recommendations into policy decisions. In addition, for those cancer types that were not yet addressed, or for which, no conclusive results could be obtained in this first round, a second round should be organised (including sarcomas, cancer of the thymus, renal cancer, cancer of the testis and the penis, complex lung surgery...). The ultimate goal is that, in the foreseeable future, each single patient with a rare or complex cancer can benefit from the best available state-of-the-art care, provided by a multidisciplinary team with demonstrated expertise in that particular domain. It is very well realised that this will take some courage and that a certain degree of resistance will have to be surmounted, but eventually, the best interest of the patient should prevail.

APPENDICES

APPENDIX 1. THE RARECARE TYPOLOGY

There is no international definition of rare cancers. However in Europe, the definition elaborated by the RARECARE network, based on an incidence threshold of **6 cases/100 000 inhabitants**, has been endorsed by several European cancer organisations, among which the Belgian Cancer Registry, and will be used in this report.[u]

The value of the threshold is of course somewhat arbitrary. Other thresholds are being used: in US, rare cancers are defined based on a threshold of 15 cases/100 000 inhabitants.[1] In France, a threshold of 3 cases/100 000 inhabitants is currently used to organize the provision of care. In the RARECARE project, experts opted not to use a lower threshold (e.g. <3/100 000[a]) in order not to exclude some cancers like glial tumours, epithelial cancers of the oral cavity, soft tissue sarcomas, because these cancers are often inadequately diagnosed and treated (in relation both to lack of knowledge and lack of clinical expertise) and clinical research is seldom performed.[2]

In addition, it should be mentioned that some common cancers have specific subtypes that are uncommon and hence require a different treatment approach than the common tumours.[3]

---

[u] This list, produced by a group of pathologists, haematologists, clinicians and epidemiologists is available on the project website (http://www.rarecare.eu/rarecancers/rarecancers.asp).

The RARECARE list works as follows. First, all cancer (common and rare cancers) are listed and hierarchically structured into three layers based on various combinations of morphology and topography codes[v] as exemplified in Table 9 for tumours of the oesophagus. Secondly, tumours are grouped into three layers (explained below).[w] And finally, layers (groups of tumours) are defined as being rare or not based on the rarity threshold (6 new cases /100 000).

Structure of the RARECARE list in three layers:

- The **bottom tier or third layer** corresponds to the WHO names of individual cancer entities and their corresponding ICD-O-3 codes, but this tier is so specific that the majority of the 585 different bottom tier entities would be considered as rare cancer. The list includes all possible cancer types, even if no single case was observed in Europe in the RARECARE study.
- Bottom tier entities were grouped into **middle tier categories** which are considered to require similar clinical management. This second layer includes 200 different cancer categories from which 182 are considered rare.
- Finally, middle tier entities were grouped into 59 **top tiers (first layer)**, considered to involve the same clinical expertise and patient referral structure, and form therefore the most appropriate basis of discussion for the organisation of rare cancer care.[4 2, 5] From the 59 different top tier categories, 41 are considered rare according to the RARECARE definition.

---

[v] The topography code indicates the site of origin of a neoplasm; in other words, where the tumour arose. The morphology code refers to the cell type that has become neoplastic and its biologic activity; in other words, it records the kind of tumour that has developed and how it behaves. (source: US National Cancer Institute).

[w] These layers are not completely exclusive, implying that a minority of cancers are counted under two categories.

Table 9 – Example of structure in three layers of the RARECARE list of rare cancers, for tumours of the oesophagus

Layer	Name	Topography code (ICD-O-3)	Morphology codes	Incidence (RARECARE)	Rare (R) based on 6/100 000 threshold
Top	**EPITHELIAL TUMOURS OF OESOPHAGUS**	C15	8000-8001, 8004, 8010-8011, 8020-8022, 8032, 8050-8076, 8078, 8082-8084, 8140-8141, 8143, 8147, 8190, 8200-8201, 8210-8211, 8221, 8230-8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8380-8384, 8401, 8430, 8440-8441, 8450, 8480-8482, 8490, 8500, 8503-8504, 8510, 8512, 8514, 8525, 8542, 8550-8551, 8560, 8562, 8571-8576, 8980	*7.51*	
Middle	**Squamous cell carcinoma with variants of oesophagus**	C15	8004, 8032, 8050-8076, 8078, 8082-8084, 8560, 8980	*3.40*	*R*
Bottom	Squamous carcinoma	C15	8070	*2.85*	*R*
Bottom	Adenosquamous carcinoma	C15	8560	*0.04*	*R*
Bottom	Squamous cell carcinoma spindle cell	C15	8004, 8032, 8074, 8980	*0.01*	*R*
Bottom	Verrucous carcinoma	C15	8051	*0.00*	*R*
Bottom	Papillary squamous cell carcinoma	C15	8052	*0.00*	*R*
Bottom	Basaloid squamous cell carcinoma	C15	8083	*0.00*	*R*
Bottom	Squamous cell carcinoma, adenoid	C15	8075	*0.00*	*R*
Middle	**Adenocarcinoma with variants of oesophagus**	C15	8140-8141, 8143, 8147, 8190, 8201, 8210-8211, 8221, 8230-8231, 8255, 8260-8263, 8290, 8310, 8315, 8320, 8323, 8333, 8380-8384, 8401, 8440-8441, 8450, 8480-8482, 8490, 8500, 8503-8504, 8510, 8512, 8514, 8525, 8542, 8551, 8571-8576	*2.85*	*R*
Middle	**Salivary gland type tumours of oesophagus**	C15	8200, 8430, 8550, 8562	*0.01*	*R*
Bottom	Mucoepidermoid carcinoma	C15	8430	*0.00*	*R*
Bottom	Adenoid cystic carcinoma	C15	8200	*0.00*	*R*
Middle	**Undifferentiated carcinoma of oesophagus**	C15	8020-8022	*0.07*	*R*

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes)

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	44	68	41	49	56	49	64
2	Squamous cell carc with variants of nasal cav and sinuses	28	50	29	36	37	28	46
2	Lymphoepithelial carc of nasal cavity and sinuses	-	-	1	2	4	3	1
2	Undiff carc of nasal cavity and sinuses	1	3	2	3	4	3	4
2	Intestinal type adenocarc of nasal cavity and sinuses	5	5	7	6	6	8	8
1	EPITHELIAL TUMOURS OF NASOPHARYNX	50	43	49	53	49	60	54
2	Squamous cell carc with variants of nasopharynx	46	38	42	52	46	56	52
2	Papillary adenocarc of nasopharynx	-	-	-	-	-	1	-
1	EPITHELIAL TUM OF MAJOR SAL GLANDS AND SAL GLAND TYPE TUM	173	211	171	194	194	183	196
2	Epithelial tum of major salivary glands	105	134	103	129	102	113	125
2	Salivary gland-type tum of head and neck	61	70	67	61	91	66	67
1	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	952	844	845	954	904	927	834
2	Squamous cell carc with variants of hypopharynx	227	203	226	266	230	268	214
2	Squamous cell carc with variants of larynx	706	632	608	686	666	650	612
1	EPITHELIAL TUMOURS OF OROPHARYNX	488	486	496	585	655	608	568
2	Squamous cell carc with variants of oropharynx	476	482	489	579	651	603	558
1	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	717	688	624	641	630	689	667
2	Squamous cell carc with variants of oral cavity	635	594	541	570	559	606	589
2	Squamous cell carc with variants of lip	76	79	72	47	53	66	58
1	EPITHELIAL TUMOURS OF OESOPHAGUS	844	890	899	925	867	898	902
2	Squamous cell carc with variants of oesophagus	471	474	485	487	479	439	481
2	Adenocarc with variants of oesophagus	347	388	390	413	371	442	402
2	Salivary gland type tumours of oesophagus	-	1	3	3	2	2	2
2	Undiff carc of oesophagus	2	4	3	6	4	3	2

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUMOURS OF STOMACH	1294	1302	1294	1242	1214	1257	1229
2	Adenocarc with variants of stomach	1251	1276	1260	1211	1181	1227	1190
2	Squamous cell carc with variants of stomach	1	6	4	8	12	9	13
2	Salivary gland-type tumours of stomach	-	-	3	1	2	4	4
2	Undiff carc of stomach	9	2	4	3	2	4	6
1	EPITHELIAL TUMOURS OF SMALL INTESTINE	82	94	93	87	77	83	92
2	Adenocarc with variants of small Intestine	65	82	83	78	74	80	85
2	Squamous cell carc with variants of small Intestine	1	-	1	2	-	-	-
1	EPITHELIAL TUMOURS OF COLON	5376	5358	5397	5411	5689	5751	5735
2	Adenocarc with variants of colon	5268	5287	5349	5355	5636	5699	5664
2	Squamous cell carc with variants of colon	2	1	3	1	3	1	-
1	EPITHELIAL TUMOURS OF RECTUM	2101	2106	2272	2289	2360	2326	2318
2	Adenocarc with variants of rectum	2077	2084	2250	2271	2342	2315	2293
2	Squamous cell carc with variants of rectum	3	7	10	5	10	3	7
2	Basaloid carc of rectum	-	2	1	1	-	-	-
1	EPITHELIAL TUMOURS OF ANAL CANAL	104	115	117	122	119	142	156
2	Squamous cell carc with variants of anal canal	82	98	92	94	96	108	118
2	Adenocarc with variants of anal canal	21	14	22	23	17	28	36
2	Paget disease of anal canal	-	-	2	2	3	-	1
1	EPITHELIAL TUMOURS OF PANCREAS	1037	1027	1138	1125	1104	1268	1391
2	Adenocarc with variants of pancreas	799	839	955	969	927	1082	1150
2	Squamous cell carc with variants of pancreas	-	1	-	-	1	-	1
2	Acinar cell carc of pancreas	3	8	11	6	4	5	9
2	Mucinous cystadenocarc of pancreas	2	3	1	3	2	4	4
2	Intraductal papillary muc carc invas of pancreas	3	-	2	9	4	8	9
2	Solid pseudopapillary carc of pancreas	1	2	-	-	3	2	1
2	Serous cystadenocarc of pancreas	-	-	-	1	-	-	-
2	Carc with osteoclast-like giant cells of pancreas	-	-	1	-	-	1	-

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUM OF LIVER AND INTRAHEPATIC BILE TRACT IBT	364	450	486	509	604	599	652
2	Hepatocellular carc of liver and IBT	275	325	323	402	461	456	470
2	Cholangiocarc of IBT	56	82	106	86	109	112	123
2	Adenocarc with variants of liver and IBT	20	14	16	1	2	2	1
2	Undiff carc of liver and IBT	-	-	-	-	-	-	-
2	Squamous cell carc with variants of liver and IBT	-	-	-	-	-	-	-
2	Bile duct cystadenocarc of IBT	2	-	-	1	-	1	-
1	EPITHELIAL TUM OF GALLBLADDER AND EXTRAHEPATIC BILIARY DUCT	335	293	320	348	346	379	389
2	Adenocarc with variants of gallbladder and EBT	289	266	293	316	308	331	317
2	Squamous cell carc of gallbladder and EBT	1	-	1	1	2	3	6
1	EPITHELIAL TUMOURS OF TRACHEA	14	14	11	16	5	16	12
2	Squamous cell carc with variants of trachea	9	10	9	11	4	11	10
2	Adenocarc with variants of trachea	3	2	1	2	1	3	1
2	Salivary gland-type tum of trachea	-	1	1	2	-	2	1
1	EPITHELIAL TUMOURS OF LUNG	7037	6981	7047	7354	7253	7554	7788
2	Squamous cell carc with variants of lung	1902	1846	1942	1917	1866	1878	1855
2	Adenocarc with variants of lung	2124	2286	2400	2540	2556	2896	2937
2	Large cell carc of lung	609	556	453	447	397	386	353
2	Well diff endocrine carc of lung	87	104	94	102	103	106	85
2	Poorly diff endocr carc of lung	1118	1084	1075	1198	1204	1152	1247
2	Bronchiolo-alveolar carc of lung	130	105	89	113	123	132	116
2	Salivary gland -type tum of lung	10	9	10	9	8	8	10
2	Sarcomatoid carc of lung	28	25	21	22	17	32	21
2	Undiff carc of lung	83	90	58	36	31	23	29

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUMOURS OF THYMUS	38	24	28	24	21	31	37
2	Malignant thymoma	34	18	24	21	18	25	30
2	Squamous cell carc of thymus	1	2	1	3	1	4	5
2	Undiff carc of thymus	-	1	1	-	-	-	-
2	Lymphoepithelial carc of thymus	-	-	-	-	-	-	-
2	Adenocarc with variants of thymus	2	-	1	-	-	1	-
1	EPITHELIAL TUMOURS OF BREAST (BOTH SEXES)	9462	9447	9533	9747	9650	9675	9960
2	Invasive ductal carc of female breast	6801	6978	7092	7271	7383	7544	7675
2	Invasive lobular carc of female breast	1234	1142	1247	1283	1254	1227	1348
2	Mammary Paget s disease of female breast	41	40	28	26	27	21	30
2	Special types of adenocarc of female breast	203	199	201	192	186	147	179
2	Metaplastic carc of female breast	21	36	43	35	46	28	23
2	Salivary gland-type tum of female breast	5	7	11	12	18	6	6
2	Epithelial tum of male breast	88	83	65	81	84	99	83
1	EPITHELIAL TUMOURS OF CORPUS UTERI	1345	1288	1250	1263	1344	1355	1278
2	Adenocarc with variants of corpus uteri	1296	1264	1227	1243	1330	1335	1255
2	Squamous cell carc with variants of corpus uteri	16	7	5	3	5	5	7
2	Adenoid cystic carc of corpus uteri	-	-	-	-	-	-	-
2	Transitional cell carc of corpus uteri	-	1	-	-	-	-	-
1	EPITHELIAL TUMOURS OF CERVIX UTERI	646	650	605	696	632	596	586
2	Squamous cell carc with variants of cervix uteri	495	516	465	570	496	472	457
2	Adenocarc with variants of cervix uteri	129	119	126	118	121	105	109
2	Undiff carc of cervix uteri	2	-	-	-	-	-	2
1	MIXED EPITHELIAL AND MESENCHYMAL TUMOURS OF UTERUS	67	72	67	65	67	63	77
1	EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE	876	904	899	884	877	783	849
2	Adenocarc with variants of ovary	662	692	694	694	657	599	670
2	Mucinous adenocarc of ovary	94	94	82	86	99	69	68
2	Clear cell adenocarc of ovary	35	30	41	32	30	21	32
2	Adenocarc with variants of fallopian tube	23	25	25	23	43	40	37

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	NON EPITHELIAL TUMOURS OF OVARY	46	49	33	43	30	39	36
2	Mixed epithelial mesenchymal tumors of ovary	18	24	16	23	9	17	16
2	Sex cord tum of ovary	14	9	7	6	8	8	5
2	Malignant immature teratomas of ovary	7	4	5	5	6	9	8
2	Germ cell tum of ovary	7	12	5	9	7	5	7
1	EPITHELIAL TUMOURS OF VULVA AND VAGINA	197	218	216	213	227	231	265
2	Squamous cell carc with variants of vulva and vagina	166	185	179	186	197	200	225
2	Adenocarc with variants of vulva and vagina	19	11	9	8	7	9	15
2	Paget s disease of vulva and vagina	1	3	4	2	6	2	6
2	Undiff carc of vulva and vagina	-	-	1	-	-	-	-
1	TROPHOBLASTIC TUMOURS OF PLACENTA	2	3	-	8	4	4	3
2	Choriocarc of placenta	2	3	-	8	4	4	3
1	EPITHELIAL TUMOURS OF PROSTATE	9732	9713	9274	8977	8840	8694	8658
2	Adenocarc with variants of prostate	9589	9598	9185	8898	8783	8603	8576
2	Squamous cell carc with variants of prostate	4	2	3	3	-	2	2
2	Infiltrating duct carc of prostate	23	14	12	11	26	26	17
2	Transitional cell carc of prostate	10	1	2	-	-	-	-
2	Salivary gland-type tum of prostate	3	20	27	32	10	10	20
1	TUMOURS OF TESTIS AND PARATESTIS	248	282	271	294	320	313	315
2	Adenocarc with variants of paratestis	-	-	-	-	-	2	-
2	Germ cell non seminomatous tumours of testis	102	116	110	129	153	151	155
2	Germ cell seminomatous tumours of testis	133	150	147	156	151	149	147
2	Spermatocytic seminoma	1	3	2	1	8	4	7
2	Teratoma with malignant transformation	-	-	-	-	-	-	-
2	Sex cord tumours of testis	3	6	2	1	5	1	5
1	EPITHELIAL TUMOURS OF PENIS	65	66	73	71	73	78	86
2	Squamous cell carc with variants of penis	63	65	72	70	70	76	83
2	Adenocarc with variants of penis	1	-	-	1	2	1	1

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUMOURS OF KIDNEY	1313	1344	1363	1388	1479	1454	1504
2	Renal cell carc with variants	1209	1276	1289	1297	1403	1378	1369
2	Squamous cell carc spindle cell type of kidney	-	-	-	-	-	-	-
2	Squamous cell carc with variants of kidney	5	4	4	3	4	1	5
1	EPITHELIAL TUMOURS OF PELVIS; URETER AND URETHRA	307	302	302	346	361	386	415
2	Transitional cell carc of pelvis; ureter and urethra	291	289	286	330	334	357	387
2	Squamous cell carc with variants of pelvis; ureter; urethra	6	8	8	11	7	9	7
2	Adenocarc with variants of pelvis; ureter and urethra	3	2	3	1	5	7	3
2	Salivary gland type tumours of pelvis; ureter and urethra	-	-	-	-	-	-	-
1	EPITHELIAL TUMOURS OF BLADDER	2045	2063	1978	2072	2153	2163	2215
2	Transitional cell carc of bladder	1946	1986	1897	2015	2093	2074	2120
2	Squamous cell carc with variants of bladder	38	22	30	23	27	41	38
2	Adenocarc with variants of bladder	24	26	29	20	22	30	29
2	Salivary gland-type tumours of bladder	-	-	-	-	-	-	-
1	EPITHELIAL TUMOURS OF EYE AND ADNEXA	8	1	1	4	9	1	3
2	Squamous cell carc with variants of eye and adnexa	6	1	1	4	8	1	2
2	Adenocarc with variants of eye and adnexa	-	-	-	-	1	-	1
1	EPITHELIAL TUMOURS OF MIDDLE EAR	6	2	4	4	2	1	1
2	Squamous cell carc with variants of middle ear	6	2	4	3	2	1	1
2	Adenocarc with variants of middle ear	-	-	-	1	-	-	-
1	MALIGNANT MESOTHELIOMA	236	258	247	246	259	234	255
2	Mesothelioma of pleura and pericardium	220	240	230	229	238	212	235
2	Mesothelioma of peritoneum and tunica vaginalis	15	18	13	17	19	21	19
1	MALIGNANT SKIN MELANOMA	1496	1565	1562	1681	1892	1882	2031
1	MALIGNANT MELANOMA OF MUCOSA	33	26	44	42	36	49	28
1	MALIGNANT MELANOMA OF UVEA	28	37	45	67	73	84	65

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	EPITHELIAL TUMOURS OF SKIN	9712	11514	13002	14690	14963	16066	17930
2	Basal cell carc of skin	7091	8755	10100	11255	11458	12337	13851
2	Squamous cell carc with variants of skin	2608	2739	2881	3433	3505	3727	4074
1	ADNEXAL CARCINOMA OF SKIN	55	70	70	81	87	79	69
1	EMBRYONAL NEOPLASMS	47	59	41	43	39	57	54
2	Neuroblastoma and ganglioneuroblastoma	16	21	14	18	14	21	22
2	Nephroblastoma	19	21	19	16	12	16	12
2	Retinoblastoma	8	16	7	9	8	16	16
2	Hepatoblastoma	2	1	1	-	3	3	3
2	Pulmonary blastoma	2	-	-	-	2	1	1
2	Pancreatoblastoma	-	-	-	-	-	-	-
1	EXTRAGONADAL GERM CELL TUMOURS	18	20	17	19	25	14	18
2	Extragonadal malignant immature teratomas	4	6	5	4	8	6	4
2	Extragonadal germ cell tumours	14	14	12	15	17	8	14
1	SOFT TISSUE SARCOMA	697	656	608	720	711	601	623
2	Soft tissue sarcoma of head and neck	47	25	29	34	43	30	19
2	Soft tissue sarcoma of limbs	123	136	120	157	178	163	148
2	Soft tissue sarcoma of superficial trunk	57	50	49	71	60	63	54
2	Soft tissue sarcoma of mediastinum	4	2	3	5	7	7	4
2	Soft tissue sarcoma of heart	2	4	1	2	2	-	3
2	Soft tissue sarcoma of breast	43	34	30	23	23	23	25
2	Soft tissue sarcoma of uterus	65	69	53	74	68	51	66
2	Other soft tissue sarcomas of genitourinary tract	31	31	25	40	32	27	25
2	Soft tissue sarcoma of viscera	29	46	42	35	52	29	28
2	Soft tissue sarcoma of paratestis	5	3	8	9	7	3	8
2	Soft tissue sarcoma of retroperitoneum and peritoneum	41	40	43	37	49	35	42
2	Soft tissue sarcoma of pelvis	1	1	-	-	-	-	1
2	Soft tissue sarcoma of skin	114	102	73	104	95	78	97
2	Soft tissue sarcoma of paraorbit	6	-	2	-	1	-	2

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
2	Soft tissue sarcoma of brain and other parts of nerv system	21	16	24	24	12	17	21
2	Embryonal rhabdomyosarcoma of soft tissue	9	5	9	11	2	6	7
2	Alveolar rhabdomyosarcoma of soft tissue	-	4	2	8	6	4	6
2	Ewing s family tumours of soft tissue	3	6	8	9	8	7	8
1	BONE SARCOMA	142	130	127	130	117	85	116
2	Osteogenic sarcoma	28	26	26	23	19	23	31
2	Chondrogenic sarcomas	47	33	36	44	40	30	33
2	Notochordal sarcomas; chordoma	8	7	8	9	5	5	9
2	Vascular sarcomas; angiosarcoma	1	1	1	1	1	-	1
2	Ewing s family of tumours	17	30	19	20	16	12	15
2	Epithelial tumours; adamantinoma	3	2	2	-	2	-	1
2	Other high grade sarc (fibrosarc; malig fibr histiocytoma)	3	2	2	2	3	3	1
1	GASTROINTESTINAL STROMAL SARCOMA	94	92	89	72	93	89	198
1	KAPOSI SARCOMA	31	32	30	39	45	51	38
1	NEURO ENDOCRINE TUMOURS	547	576	623	642	685	731	756
2	Well diff endocr tumours; carcinoid	36	44	55	39	58	61	43
2	Well diff endocr tumours; atypical carcinoid	2	4	4	2	1	3	5
2	Poorly diff endocr carc (lung small cell carc excluded)	104	108	121	122	120	135	105
2	Mixed endocrine-exocrine carcinoma	3	1	1	5	8	5	8
2	Endocr carc thyroid gland	34	40	34	36	44	41	42
2	Well diff not funct endocr carc of pancr and digest tract	312	321	348	372	385	406	478
2	Well diff funct endocr carc of pancreas and digest tract	5	4	2	5	4	5	8
2	Endocr carc of skin	49	51	54	60	61	71	67
1	CARCINOMA OF ENDOCRINE ORGANS	620	654	688	688	750	879	859
2	Carc of pituitary gland	3	3	5	1	2	1	6
2	Carc of thyroid gland	590	628	648	660	714	849	806
2	Carc of parathyroid gland	1	1	8	1	6	3	2
2	Carc of adrenal gland	16	17	23	25	23	22	39

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	GLIAL TUMOURS OF CNS AND PINEAL GLAND	715	693	676	705	724	797	736
2	Astrocytic tumours of CNS	598	586	587	601	642	695	648
2	Oligodendroglial tumours of CNS	87	77	58	72	51	66	55
2	Ependymal tumours of CNS	30	30	31	32	31	35	33
1	NON GLIAL TUMOURS OF CNS AND PINEAL GLAND	23	23	37	23	26	27	29
2	Embryonal tumours of CNS	20	21	33	21	26	26	28
2	Choroid plexus carc of CNS	3	2	4	2	-	1	1
1	MALIGNANT MENINGIOMAS	28	16	13	10	13	11	15
1	GLIAL TUM OF CRAN AND PERIP NERV; AUT NERV SYS AND PARAGANG	-	1	1	3	-	-	3
2	Astrocyt tum of cran and perip nerv; aut nerv syst; paragan	-	1	-	1	-	-	-
2	Ependym tum of cran and perip nerv; aut nerv syst and parag	-	-	1	2	-	-	3
1	NON-GLIAL TUM OF CRAN AND PERIP NERV; AUT NERV SYS AND PARAG	11	9	10	13	8	17	9
2	Embryonal tum of cran and perip nerv; aut nerv sys; paraga	8	8	8	12	5	9	7
2	Paraganglioma	3	1	2	1	3	8	2
1	LYMPHOID DISEASES	3795	3633	3661	3786	3862	3933	4023
2	Hodgkin lymphoma	288	301	292	272	310	305	308
2	Precursor B/T lymphoblastic leuk/lymphoblastic lymphoma	187	170	164	190	201	186	194
2	Tcutaneous lymphoma	90	95	69	102	101	99	97
2	Other T cell lymphomas and NK cell neoplasms	102	118	138	127	134	155	149
2	Diffuse and follicular B lymphoma	957	947	1011	1094	1077	1117	1138
2	Hairy cell leukaemia	43	51	37	43	53	43	43
2	Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	748	682	714	751	728	755	754
2	Other non Hodgkin; Mature B cell lymphoma	1079	999	1011	1081	1120	1133	1216
1	ACUTE MYELOYD LEUKAEMIA AND RELATED PRECURSOR NEOPLASMS	403	437	388	475	451	456	514
2	Acute promyelocytic leuk (AML with t(15;17) with var...	7	17	11	19	14	16	25
2	AML	384	413	368	452	429	437	476

Table 10 – Rare cancers: Number of new diagnoses by incidence year, Belgium 2004-2010 (both sexes) - continued

Layer	Label	2004	2005	2006	2007	2008	2009	2010
1	MYELOPROLIFERATIVE NEOPLASMS	432	453	439	536	527	552	637
2	Chronic myeloid leukemia	143	141	118	156	143	142	179
2	Other myeloproliferative neoplasms	286	306	312	367	374	398	444
2	Mast cell tumours	3	6	9	13	10	12	14
1	MYELODYSPLASTIC SYND AND MYELODYSP/MYELOPROLIFERATIVE DIS	566	539	527	529	685	659	676
2	Myelodysplastic syndrome with 5q syndrome	5	11	6	9	7	12	8
2	Other myelodysplastic syndrome	461	441	411	404	535	529	530
2	Chronic Myelomonocytic leukemia	41	32	35	61	73	58	67
2	Atypical chronic myeloid leukemia BCR/ABL negative	9	11	20	10	9	5	11
1	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	13	6	15	9	19	13	39

Source: Belgian Cancer Registry

APPENDIX 2. ORGANISATION OF CARE IN ONCOLOGY IN BELGIUM

Appendix 2.1. Care provision

Appendix 2.1.1. Basic programmes and specialized programmes in oncology

Certification requirements

Common topics between these two programmes include the staffing requirements for nurses and paramedics and the necessary multidisciplinary approach to manage the patients pathway. The difference between the two programmes lies mainly in the amount of supervision and in the infrastructure required and surrounding elements.

Nursing practitioners have to attest an expertise in oncology. For basic programmes, nursing acts have to be provided under the surveillance of nurses with required expertise. For chemotherapy, a particular professional competency or some years of professional experience are required. This also applies to radiotherapy.

A multidisciplinary team for psychosocial support should be available in each centre. This activity can also be endorsed by the multidisciplinary team who is responsible for palliative support.

Moreover, a specialist in pain control, a physiotherapist, a dietician and a specialist in pathology have to be available in each centre (potentially via an association or a care program in oncology).

Both programmes need to have a medical coordinator. For basic programmes in oncology, this physician has to be specifically experienced in oncological treatments and employed on a full-time basis at the centre; s/he is responsible for the coordination of the activities of all specialists involved in the cancer treatment in the centre. For specialized programs in oncology, the required staffing and expertise are higher. Specialists from the following disciplines are needed:

- at least one full-time certified specialist in internal medicine who has the professional title in oncology;
- at least one specialist in radiotherapy-oncology, possibly as consultant in the radiotherapy service from another hospital having signed a collaboration agreement;
- specialists in surgery with a professional title in oncology or with an oncological activity in their specialty, having at least 3 years of experience in the management of neoplastic diseases;
- at least one specialist in internal medicine with the professional title of clinical haematology, possibly as consultant;
- at least one certified specialist with the professional title in oncology for three among the four following specialties: gastro-enterology, pneumology, gynaeco-obstetrics and urology;
- specialists in pathology, clinical biology and radiology, working full-time in hospital with the specialized programme in oncology, and reachable at all times.

Specialists other than those cited above having a professional title in oncology or having a large oncological activity are fully involved in the framework of the care programme in oncology.

Moreover, the centre needs to fulfil the following requirements:

- having 24h/24 a physician available who can identify and treat oncological emergencies;
- a specialist certified in internal medicine with a professional title in oncology (potentially assisted by a specialist with enough experience in the management of toxic and infectious complications induced by chemotherapy) and a specialist in radiotherapy-oncology reachable at all times.

Additional obligations in terms of infrastructure and surrounding elements are required for specialized programmes in oncology:

- the availability of a radiotherapy service, either in the hospital or in another hospital having signed a convention for collaboration;
- the availability of a certified intensive care service in the same hospital;
- the availability of a medical oncology hospitalization unit for the administration of systemic therapies;

- the availability of equipments allowing the adequate and safe administration of chemotherapy in day hospitalization, with a possibility to reach specialists from the care in oncology 24h/24;
- the inclusion of a Pharmacy and Therapeutics Committee a working group, that specifically deals with the handling of anti-tumour medication and the drafting of guidelines for the preparation and administration of these drugs. The preparation should be carried out in an environment specially adapted and dedicated for that purpose, under direct supervision of a hospital pharmacist responsible for controlling the prescribed dosage.

Certification of different sites within a hospital

A care programme in oncology that is geographically dispersed on different sites has to identify only one medical coordinator, one multidisciplinary oncological manual and only one oncological multidisciplinary commission. Care programmes in oncology can be split up into different sites for a same hospital or into different hospitals. Every site has to fulfil all legal obligations.

APPENDIX 3. EVIDENCE OF DISPERSION OF CANCER CARE IN BELGIUM

Appendix 3.1. Oesophagectomies

Nomenclature codes used in this study:

- (228023) Oesophagectomie ou gastro-oesophagectomie thoracique ou thoraco-abdominale, en un temps avec reconstitution de la continuité
- (228185) Oesophagectomie subtotale jusqu'au niveau de la crosse aortique, avec reconstitution de la continuité
- (228244) Oesophagectomie ou gastro-oesophagectomie thoracique ou thoraco-abdominale, en un temps avec reconstitution de la continuité et évidement ganglionnaire étendu
- (228266) Oesophagectomie subtotale jusqu'au niveau de la crosse aortique, avec reconstitution de la continuité et évidement ganglionnaire étendu

Table 11 – Evolution of number of oesophagectomies, by code, year and volume of hospitals

By code	2007	2008	2009	2010	2011	2012*
228023	62	71	60	55	60	47
228185	391	356	361	377	244	120
228244					14	42
228266					128	307
Total	**453**	**427**	**421**	**432**	**446**	**516**
N hospitals	**71**	**75**	**64**	**67**	**64**	**66**
Mean volume	**6.4**	**5.7**	**6.6**	**6.4**	**7.0**	**7.8**
Median volume	**3**	**3**	**3.5**	**3**	**4**	**4**
P75 volume	**5**	**6**	**7**	**7**	**6.5**	**9**

**Data 2012 not complete*

Appendix 3.2. Pancreatectomies

Nomenclature codes used in this study:

- (242023) Duodéno-pancréatectomie
- (242045) Hémi-pancréatectomie gauche avec anastomose jéjunale de la tranche de section ou pancréatectomie quasi totale (95%)
- (242060) Hémi-pancréatectomie gauche ou énucléation d'une tumeur du pancréas ou ablation d'un séquestre pancréatique

Table 12 – Evolution of number of pancreatectomies, by code, year and volume of hospitals

By code	2007	2008	2009	2010	2011	2012*
242023	421	400	454	441	466	455
242045	74	74	78	65	74	69
242060	221	179	185	172	254	205
Total	**716**	**653**	**717**	**678**	**794**	**729**
N hospitals	**82**	**86**	**89**	**93**	**91**	**87**
Mean volume	**8.7**	**7.6**	**8.1**	**7.3**	**8.7**	**8.4**
Median volume	**3.5**	**4**	**4**	**3**	**4**	**4**
P75	**7**	**7**	**7**	**7**	**8**	**9**

**Data 2012 not complete*

Appendix 3.3. Colectomie for FAP patients

Nomenclature codes used in this study: 244764- Proctocolectomie ou colectomie de restauration avec construction d'un réservoir iléal, mise en place d'une anastomose iléo-anale et éventuelle iléostomie proximale temporaire

Table 13 – Evolution of procedure 244764 over time, and volume per hospital

Code 244764	2007	2008	2009	2010	2011	2012*
Total	211	145	136	113	108	106
Number of hospitals	37	35	31	28	31	31
Mean per hospital	5.7	4.1	4.4	4.0	3.5	3.4
Median per hospital	1	1	1	2	1	1
P75	3	3	5	3	2	2

**Data 2012 not yet complete*

Appendix 3.4. Debulking

Nomenclature codes used in this study:

- (244963 - 244952) Traitement chirurgical complet avec omentectomie, résection de tous les organes tumoraux et un debulking cytoréducteur minutieux du péritoine

Table 14 – Evolution of procedure 244963 over time, and volume per hospital

Code 244963	2007	2008	2009	2010	2011	2012*
Total procedures	-	-	-	77	197	231
Number of hospitals	-	-	-	17	33	35
Mean per hospital	-	-	-	4.5	6.0	6.6
Median per hospital	-	-	-	1	2	2
P75	-	-	-	4	4	6

**Data 2012 not yet complete*

Appendix 3.5. HIPEC

Nomenclature codes used in this study:

- (244985 – 244974) Chimiohyperthermie intrapéritonéale (HIPEC) peropératoire, en complément de la prestation 244952-244963, pour l'ensemble des lavages

Table 15 – Evolution of procedure 244985 over time, and volume per hospital

Code 244985	2007	2008	2009	2010	2011	2012*
Total procedures	-	-	-	38	123	159
Number of hospitals	-	-	-	9	15	17
Mean per hospital	-	-	-	4.2	8.2	9.4
Median per hospital	-	-	-	1	4	4
P75	-	-	-	6	10	10

**Data 2012 not yet complete*

APPENDIX 4. EUROPEAN PROJECTS ON SURVEILLANCE, RESEARCH AND ORGANISATION OF CARE

Appendix 4.1. The RARECARE project and RARECARENet

The RARECARE project is a European project on the **surveillance** of rare cancers in Europe (www.rarecare.eu). The Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) is the leading organisation and more than 15 European Institutions and Organisations participate in the project as associated or collaborating partners. Belgium is represented by the Belgian Cancer Registry, which collaborates to the definition and the operationalisation of the rare cancer registry. RARECARE was co-funded by the European Commission (EC) from 2007 to 2010 through its Public Health and Consumer Protection Directorate (DG SANCO), PHEA programme, and contributes among other projects to the creation of networks of action for rare diseases. This project is also supported by the Executive Agency for Health and Consumers (EAHC) of the European Commission.

Its **objectives** are (a) to provide an operational definition of “rare cancers”, based rather on tumour incidence than on tumour prevalence, (b) to compile a list of cancers that meet this definition, (c) to provide cancer burden indicators (incidence, survival, prevalence and mortality), based on population-based cancer registry data, on rare cancers across Europe, (d) to improve the quality of data on rare cancers and (e) to develop strategies and mechanisms for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers.

Recently, Rare Cancers Europe has joined as collaborating partner RARECARENet, an information network on rare cancers which is funded in the framework of the Second EU Health Programme[6]. The project, launched in July 2012, aims at improving the timeliness and accuracy of diagnosis, facilitating access to high quality treatment for patients with rare cancers, identifying centres of expertise for rare cancers and establishing a related information network across Europe. More specifically, its objectives are:

- To describe diagnosis and treatment pathways from registry data;
- To identify the qualification criteria for centres of expertise and list centres of expertise;
- To produce and disseminate information on diagnosis and management of rare cancers;
- To develop a clinical database on very rare cancers to develop new knowledge on their clinical management.

The partners of the RARECARENet project also intend to develop - in collaboration with the European Society for Medical Oncology (ESMO) - new clinical practice guidelines on rare cancers, which have not been addressed yet. Belgium is represented by the Belgian Cancer Registry.
At present the Belgian Cancer Registry is involved in two studies coordinated by the RARECARENet. The first study is a high resolution study in order to identify qualification criteria for centres of expertise for some specific types of rare cancers (i.e. NETs, testis, head and neck and sarcoma's). The second is a volume study where the impact of hospital volume on cancer outcomes are analysed.

Appendix 4.2. Rare Cancers Europe - European Action Against Rare Cancers

Rare Cancers Europe is a joint initiative based on a partnership between the European Society for Medical Oncology (ESMO), the European Organisation for Rare Diseases (EURORDIS), the European Cancer Patient Coalition (ECPC), the European Organisation for Research and Treatment of Cancer (EORTC), and many other stakeholders in rare cancers and rare diseases (http://www.rarecancerseurope.org/). The collaboration began in 2008 in relation to the organisation of the conference "Rare Tumours in Europe: Challenges and Solutions". Since then, the organisations have continued to work together and more organisations have joined.

Its **objectives** are to address challenges and propose solutions to eliminate the barriers that patients with rare cancers, researchers, medical professionals and the pharmaceutical industry working in this field face every day. During the congress **a set of** 39 recommendations on stakeholder actions and public policies **was developed (see**

Recommendations from the European Society for Medical Oncology).[7]

Since 2008 Rare Cancers Europe campaigned to implement the 39 recommendations and to put rare cancers firmly on the European policy agenda. In 2012 the European Society for Medical Oncology (ESMO) and Rare Cancers Europe organised the Rare Cancers Conference, which provided a multi-stakeholder platform for rare cancer and rare disease experts from across Europe to exchange views and share insights into what can be done to improve the methodology of clinical research on rare cancers. The views and suggestions of all stakeholders are summarized in a consensus paper, which can be used for related advocacy efforts.

Appendix 4.3. European Partnership for Action Against Cancer (EPAAC)

The European Partnership for Action Against Cancer is a five-year initiative taking place under the umbrella of the European Commission to fill a void in cooperation, collaboration and shared experiences among countries with similar needs and diverse experiences in the field of national cancer control policy. Activities and studies will tackle the main challenges of cancer control in Europe and in Member States, including service provision and health system responses, human resources and research. The European Partnership for Action Against Cancer (EPAAC) was launched in 2011, after the European Commission published its Communication on Action Against Cancer: European Partnership (see http://www.epaac.eu/home). The Partnership brings together the efforts of different stakeholders into a joint response to prevent and control cancer. In its initial phase, until early 2014, the work of the Partnership will be taken forward through a Joint Action (co-financed by the EU Health Programme).

The important technical work packages in the Partnership are the following:

- Health Promotion and Prevention (Work Package 5);
- Screening and Early Diagnosis (Work Package 6);
- Identification and dissemination of good practice in healthcare (Work Package 7);
- Cancer research (Work Package 8);
- Health information and data (Work Package 9);
- National Cancer Plans (Work Package 10).

The rationale of the WP7 is the comprehensive evidence about a European variability in both delivery of services and outcomes of care. According to EPAAC, key elements for better cancer care consist of the following: rapid access to diagnosis, multidisciplinary care, coordination of cancer care throughout the process from diagnosis to therapy, including palliative care, provision of psychosocial care services, consideration of patient preferences in the clinical decision-making process and use of evidence-based therapeutic guidelines. This includes concentration of diagnostic and therapeutic procedures of low frequency or high complexity in services with adequate caseload and audited results, and evaluation of outcomes. There are examples of good practices aimed at improving cancer care aligned with these elements across European health services, at national, regional and local level, which should be identified, and experiences exchanged in the framework of this Action.

Work package 7 will have a particular focus on **new organisational perspectives in cancer care**, specifically networks of cancer care at regional level and for low frequency tumours. Evidence also suggests that evidence-based guidelines in cancer are often not put into practice, hampering improvement in cancer care and patient outcomes.

Appendix 4.4. A European reference network: Organisation of European Cancer Institute's (OECI)

The «Organisation of European Cancer Institute's» is a structure aimed at improving the quality of cancer care and translational research in Europe from an organisational viewpoint by fostering an efficient partnership across Europe, notwithstanding its linguistic barriers and traditional research heterogeneity.

In 2005 the Organisation was remodelled into the Organisation of European Cancer Institute's, European Economic Interest Grouping (OECI-EEIG). It regroups 73 cancer centres and institutions across Europe, among which 3 Belgian hospitals (Institut Jules Bordet, Brussels; Oncologic Center, UZ Brussel, Brussels ; Cliniques universitaires Saint-Luc (Centre du Cancer), Brussels). This European network encompasses

27 countries (which are not the 27 Members States of the European Union).

Four working groups are conducting focused expertise projects:

1. **The Accreditation/Designation Working Group** is defining consensual quality standards and criteria for European oncology, and is developing a tool which enables the internal as well as the external assessment of the performances of the cancer institutions. A detailed database of the cancer centres' infrastructure and human resources will be developed, in order to indentify the structures where the accelerated development of innovative treatments or of high-quality clinical research is feasible. The establishment of criteria for the European Comprehensive Cancer Centres and the harmonisation of their resources in order to reach a critical mass for research are important goals.
2. **The Molecular Pathobiology Working Group** aims at updating and promoting new developments in histopathology, cytology and molecular testing in the field of cancer. The working group focuses on education, training and the unification of criteria in Cancer Institute's to become up to date with these new approaches in cancer diagnosis (biobanks, data storage and transfer, immunohistochemistry, and FISH among others).
3. **The European Cancer Biobank Working Group** aims at establishing an efficient infrastructure for OECI multi-centre research platforms, providing request options for samples collected from cancer patients for translational and clinical research for cooperative multi-centre research adopting agreed rules for access and exchange.
4. **The Education and Training Working Group** aims at coordinating and implementing the educational activities of the European Cancer Institutes.

Appendix 4.4.1. Accreditation and designation of cancer centres

Oncology was seen by the OECI as a speciality particularly suited to experimenting a first application of accreditation at a European level. The OECI launched the Accreditation Project in September 2005, and gave mandate to the Accreditation Working Group (AWG) to lead this project, following three objectives:

- to develop a comprehensive accreditation system for oncology care, taking into account prevention, care, research, education and networking.
- to set an updated database of cancer centres in Europe, with exhaustive information on their resources and activities (in care, research, education and management).
- to develop a global labelling tool dedicated to comprehensive cancer centres in Europe, designating the various types of cancer structures, and the comprehensive cancer centres of reference and Excellence.

The Working Group established:

- standards and criteria for quality multidisciplinary cancer care delivered in cancer centres throughout Europe (Quality Manual),
- a process allowing to survey the cancer centres in order to assess compliance with these standards,
- a quantitative questionnaire measuring the resources and activities in the cancer centres,
- a tool to collect standardised and qualitative data from approved cancer centres, to measure treatments patterns and outcomes. The tool is translated into an electronic format (OECI accreditation e-Tool).

OECI has specialised its Accreditation & Development (A&D) programme on multidisciplinary, global and integrated cancer care and research with a major focus on comprehensiveness. The accreditation tool allows health care organisations to support their performance improvement and to demonstrate their accountability to the public and other stakeholders. Each hospital/centre can assess the effectiveness of all corrective actions, identify their own areas of excellence and compare their performance with that of peer institutions using the same measures. Similarly, performance data can be used by external stakeholders to make value-based decisions

on where to seek quality health care. They may provide a basis for defining centres of reference in Europe, especially for **rare cancers**.

The OECI accreditation programme is based upon the OECI standards for high qualitative cancer care, that were validated through pilot projects. The standards are translated in two questionnaires, a qualitative and a quantitative, to assess the current quality provided by a cancer centre. Both are integrated in an electronic tool (e-tool) for self-assessment (see http://oeci.selfassessment.nu/cms/node/53). Moreover, an OECI peer review visit, i.e. a systematic and independent examination, is organised to determine whether on a level of quality and the coherent results, activities correspond to the planned measures, and whether these measures are suitable and have been effectively implemented to achieve the objectives of the organisation.

The accreditation process is likely to take an average of 9 to 12 months, and longer in some cases. The self-assessment system provides a tool for estimating the readiness of the centre.

Appendix 4.4.2. Types of cancer centres

Four different types of cancer centres or organisations will be distinguished according the comprehensiveness of the services and the degree of specialisation.

1. 'Cancer Units' are defined as clinical facilities or hospital departments covering at least radiotherapy and medical or surgical oncology. Additionally they have a formalized collaboration with other hospital specialties.
2. The 'Clinical Cancer Centre' is characterised by the clinical capacity covering a sufficient degree of all medical, surgical and radiotherapy services and occasionally a limited degree of clinical research.
3. The 'Cancer Research Centre', is characterised by the capacity in cancer research focusing on one or more areas in the field of fundamental and translational oncology.
4. For the 'Comprehensive Cancer Centre' (CCC), the following features are considered to be essential:

- A highly innovative character and multidisciplinary approach using the potential of basic, translational and clinical research and clinical facilities and activities, organised in a sufficiently identifiable entity,
- A direct provision of an extensive variety of cancer care tailored to the individual patient's needs and directed towards learning and improving the professional, organisational and relational quality of care,
- Broad activities in the area of prevention, education, and external dissemination of knowledge and innovation. In order to accentuate the differences with other cancer centres, a CCC separates itself in the following points:
  - o High level of infrastructure, expertise and innovation in the field of oncology research,
  - o Maintenance of an extensive network including all aspects of oncology treatment and research,
  - o Related to an academic/university centre or is an academic centre.

Appendix 4.5. International Rare Cancer Initiative (IRCI)

International Rare Cancer Initiative (IRCI) is an international collaboration, launched in 2011, to boost the development of new treatments for patients with rare cancers; its partners are the European Organisation for Research and Treatment of Cancer (EORTC), Cancer Research UK (CR-UK), the National Institute for Health Research (NIHR) Cancer Research Network (NCRN), and the United States National Cancer Institute (NCI) (http://www.irci.info/). The objective of the IRCI is to facilitate the development of **international clinical trials** for patients with rare cancers – defined as those with an annual crude incidence of <2/100 000 - in order to boost the progress of new treatments for these patients[8]. So far, nine rare cancers have been selected for international collaborations and the potential for development of an interventional (preferably randomised) clinical trial[x].

[x] The following nine rare cancers currently form the core activities of the IRCI: head and neck cancer (specifically: salivary gland cancer and anaplastic thyroid cancer), small bowel adenocarcinoma, gynaecological sarcoma, fibrolamellar hepatocellular carcinoma, penile cancer, thymoma, ocular melanoma and relapsed/metastatic anal cancer.

Appendix 4.6. European Union Committee of Experts on Rare Diseases (EUCERD)

The European Union Committee of Experts on Rare Diseases, established in November 2009, replaces the European Commission's Rare Diseases Task Force (RDTF), which was established in 2004. The members of the **RDTF** included rare disease research project leaders, experts from member states and representatives from relevant international organisations (DG Research, DG Enterprise, EuroStat, EMA, WHO, OECD). The RDTF initiated key collaborative rare diseases initiatives in Europe and many key topics were brought forward for discussion in relation to rare disease research, policy and actions. Various working groups produced reports, recommendations and scoping papers. The RDTF played a major role in drafting "Communication Rare Diseases: Europe's Challenges", which ultimately resulted in the adoption of the **European Council Recommendation on an Action in the Field of Rare Diseases** in June 2009.

The European Union Committee of Experts on Rare Diseases (**EUCERD**) is charged with the surveillance of initiatives and incentives in the field of rare diseases at European level and at member state level (http://www.eucerd.eu/). Belgium is represented by the Federal Service of Health, Food Chain Safety and Environment, Directorate-General for the Organisation of Health Care Establishments. EUCERD decided to concentrate its activities on the **organisation of expertise** at national level including the following topics:

- the models of organisation of expert care at national level according to country size (health care pathways versus a system of coordinating centres and expert centres);
- defining the scope of expert centres in terms of disease coverage and links with university hospitals and medical specialties including reflections on recommendations for organisation by size of country;
- quality designation criteria for national centres of expertise for rare diseases in view of the experiences of Member States.

APPENDIX 5. INITIATIVES TAKEN BY SOME EUROPEAN MEMBER STATES

The following pages give an overview by country of initiatives taken to organise the care of patients with rare and complex tumours.

Appendix 5.1. France[y]

Rare cancers are defined as cancers which are diagnosed in fewer than **6/100 000 persons per year**, or requiring highly specialised management, due to their unusual location or their occurrence at a specific or complex site.

The second French National Plan for Cancers (2009-2013) adopted a specific measure on rare cancers, which aims to structure the patient pathway for rare malignant tumours. One of the suggested concrete actions is to certify rare cancer reference centres (Action 23.1).[9]

Appendix 5.1.1. Combining expertise and proximity

The organization of care for rare cancers aims to combine expertise and proximity. Each patient affected by a rare cancer should benefit from management in the institution of his/her choice, but being assured of a definitive diagnosis through the double reading of slides, discussion of his/her file by several experts in different disciplines towards a multidisciplinary team (MDT) meeting at a regional or a national level, a choice of appropriate treatments— often innovative in the context of a clinical trial—and the support of a patients' association.

Appendix 5.1.2. Structure of healthcare services

In 2009, the French National Cancer Institute (l'Institut National du Cancer, INCa) has set up a new structure of healthcare services for adults with rare cancers: for a number of rare tumours health care provision is organized for the whole country around **centres of expertise**. This new organization aims at ensuring optimal care, which involves national and regional centres

[y] The paragraphs on initiatives taken in France were reviewed and approved by Frédérique Nowak, Head of the Innovation Department, National Cancer Institute, France.

of expertise, oncology teams working in authorized institutions and patients' associations. For a given group of rare cancers, the management of affected patients relies on regional or interregional expert centres that cover the whole national territory and are coordinated at the national level by a single national expert reference centre under the supervision of a single coordinating clinician.

Regional or interregional expert centres

Regional or interregional expert centres are health institutions authorised to treat patients for cancer. The criteria for selection include multidisciplinarity, activity in relation to rare cancers, involvement in research, and publications. One clinician in charge is nominated for each regional or interregional expert centre.

The regional or interregional expert centres are responsible for the following 4 missions:

- to establish a regional or interregional referral MDT meeting. Case files of patients with rare cancers are discussed at diagnosis, when a treatment decision is being made, during follow-up, or when the disease recurs;
- to participate in clinical research, promoting the inclusion of patients with rare cancers in clinical trials;
- to participate in training of health care providers and in providing information to patients and those close to them at the regional or interregional level;
- to develop coordination with institutions authorised to treat cancer in their region, so as to enable patients to access this continuum of care, while respecting the unique features of each case.

National expert centres

The national expert centres fulfil the following missions:

- to select and set up the regional or interregional expert centres;
- to organise, if required, a referral MDT meeting at national level;
- to promote research on rare cancers through multicentre research studies at national or international level;
- to participate in drafting or updating national recommendations for good clinical practice, drawing on European or international recommendations where necessary;
- to contribute to the epidemiological surveillance and observation of these cancers by establishing a database for the collection of relevant data and the monitoring of patients, thus enabling public health studies;
- to participate at the national level in the training of health care providers;
- to participate in providing information to patients and those close to them, by developing relationships with national patients' associations, and by involvement in communication to the public at large on this rare cancer;
- to establish and monitor activity indicators for all the expert centres, ensure their collection, and send them to the INCa in the context of an annual monitoring report;
- to liaise with the national reference pathologist to integrate double reading into this structure.

The new structuring of healthcare services for **adult patients with rare cancers** is implemented step by step, through a call for applications launched by INCa. Only teaching hospitals that were authorized for the treatment of cancer (i.e. Centre Hospitalier Universitaire (CHU) and Centre de Lutte Contre le Cancer (CLCC)) are eligible as national centres of expertise. The proposals received are subjected to a double expert assessment, involving international experts.

From 2011 on, 17 cancer groups benefited from such organization of care (Table 16). Each national reference centre must set up a network with regional centres of excellence. This structure will enable the centres to provide optimal care to patients, offering both the expertise of a reference centre and the local care of a centre of excellence.

Table 16 – Existing centres of expertise in 2011

Rare cancer groups NETWORK ACRONYM	Rare cancers	National coordinating centre	Estimated annual incidence
Soft tissue and visceral sarcomas **NETSARC**	- Gastrointestinal stromal tumours (GIST) - Liposarcomas - Leiomyosarcomas - Other differentiated sarcomas - Poorly differentiated sarcomas - Unclassified sarcomas - Pulmonary, cardiac and other visceral sarcomas - Desmoid tumours	Centre Léon Bérard, Lyon	4 000 cases / year
Rare sporadic and hereditary malignant endocrine tumours **RENATEN**	- Digestive tract and pancreatic ET - Typical and atypical bronchial carcinoid type ET - Large cell neuroendocrine carcinomas - Thymic endocrine carcinomas - Other endocrine tumours (bladder, kidney, skin, etc.) - Medullary thyroid carcinomas - Sporadic malignant nonadrenal paragangliomas and familial paragangliomas	Hôpital de La Timone, AP-HM	1 200 cases / year
Rare ENT cancers **REFCOR**	- Malignant tumours of the facial bones - Malignant tumours of the salivary glands - Malignant tumours of the ear - Head and neck sarcomas - Others	Institut Gustave Roussy, Villejuif	900 cases / year
Malignant pleural mesotheliomas **MESOCLIN**		Centre Hospitalier Régional Universitaire, Lille	900 cases / year
Cutaneous lymphomas **GFELC**	- Cutaneous T cell lymphomas - Cutaneous B cell lymphomas	Hôpital Saint-Louis, AP-HP	700 cases / year
	- Anaplastic oligodendrogliomas	Hôpital Pitié-Salpêtrière, AP-HP	600 cases / year

Rare cancer groups NETWORK ACRONYM	Rare cancers	National coordinating centre	Estimated annual incidence
Rare high-grade oligodendroglial cerebral tumours **POLA**	- Anaplastic oligoastrocytomas - Glioblastomas with aoligodendroglial component		
Rare ovarian cancers **OBSERVATORY FOR RARE MALIGNANT GYNAECOLOGICAL TUMOURS**	- Mucinous adenocarcinoma - Malignant sex cord stromal tumours - Malignant germinal tumours - Clear-cell adenocarcinoma - Small cell cancers with hypercalcaemia - Endocrine tumours ostruma ovarii	Centre Léon Bérard, Lyon	500 cases / year
Cancers occurring during the pregnancy **CALG**	- Breast cancers - Malignant haemopathies - Cervical cancers - Ovarian cancers - Digestive tract cancers - Others	Hôpital Tenon, AP-HP	500 cases / year
Refractory thyroid cancer **TUTHYREF**	- Iodine 131 refractory papillary and follicular cancers - Metastatic medullary cancers - Anaplastic cancers	Institut Gustave Roussy, Villejuif	400 cases / year
Primitive lymphomas of the central nervous system **LOC**	- Primitive lymphomas of the brain, spinal cord, meninges and eye - Isolated primitive intraocular lymphomas	Hôpital Pitié-Salpêtrière, AP-HP	300 – 400 cases / year
Lymphomas associated with coeliac disease **CELAC**	- Low-grade T-cell lymphomas (clonal refractory sprue) - High-grade T-cell lymphomas - High-grade B-cell lymphomas	Hôpital européen G. Pompidou, AP-HP	350 cases / year
Malignant thymomas and thymic carcinomas **RYTHMIC**	- Malignant thymomas - Thymic carcinomas	Institut Gustave Roussy, Villejuif	250 cases / year
Gestational trophoblastic tumours	- Invasive moles	Centre hospitalier Lyon Sud,	180 cases / year

Rare cancer groups NETWORK ACRONYM	Rare cancers	National coordinating centre	Estimated annual incidence
MTG	- Choriocarcinomas - Tumours at the placental implantation site - Epithelioid trophoblastic tumours	Hospices Civils de Lyon	
Von Hippel-Lindau disease and hereditary predisposition to kidney cancer **PREDIR**	- VHL disease - Type 1 hereditary papillary carcinoma - Birt-Hogg-Dubé syndromes - Hereditary leiomyomatosis with papillary renal carcinoma - Clear cell renal carcinomas associated with translocations - Familial forms of clear cell renal carcinomas not associated with the VHL gene - Bourneville's tuberous sclerosis and renal cancer - MODY 5 diabetes and renal carcinoma	Hôpital Bicêtre, AP-HP	160 – 240 cases / year
Rare peritoneal cancers **RENAPE**	- Pseudomyxomas - Peritoneal mesotheliomas - Primitive peritoneal serous carcinomas - Peritoneal desmoplastic tumours - Peritoneal psammocarcinomas	Centre hospitalier Lyon Sud, Hospices Civils de Lyon	130 – 180 cases / year
Adrenal cancer **COMETE**	- Adrenocortical carcinomas - Malignant phaeochromocytomas - Malignant paragangliomas	Hôpital Cochin, AP-HP	100 – 150 cases / year
Virally induced cancers in transplant recipients (TR) **K-VIROGREF**	- Lymphoproliferative disorders in TR - Kaposi's sarcomas in TR - Anogenital cancers in TR - Merkel cell tumours in TR	Groupe hospitalier Pitié-Salpêtrière, AP-HP	100 – 110 cases / year

AP-HP: Assistance Publique – Hôpitaux de Paris; AP-HM: Assistance Publique – Hôpitaux de Marseille.

In 2012 the organization of care was finalized with the identification of six other clinical national expert centres, bringing the number of rare cancers benefiting from this specific organization to 23 (Table 17).

Table 17 – Clinical national expert centres installed in 2012

Rare cancers	National coordinating centre (one or several sites)
Rare renal cancers	Institut Gustave Roussy, Villejuif
Rare CNS cancers	Centre Hospitalier Universitaire, Bordeaux
Rare skin cancers	Centre Hospitalier Universitaire, Lille
Bone sarcomas	Centre Hospitalier Universitaire, Nantes
Cancers in HIV positive patients	Hôpital Pitié-Salpêtrière, AP-HP Hôpital Sainte-Marguerite, AP-HM Hôpital Antoine Béclère, AP-HP
Uveal melanomas	Institut Curie, Paris

A report of the 2011 activities of the centres recognized as centres of expertise was recently published (concerning 15 cancer groups).[10] In 2011, more than 5 500 patients who were diagnosed with one of the 15 concerned rare cancers, benefited from the organisation through clinical expert centres.[10]

National anatomopathological reference networks

In addition, 3 anatomopathological reference networks were set up for the following rare cancer groups:

- soft tissue and visceral sarcomas (RRePS-TMV)
- malignant pleural mesotheliomas and rare peritoneal tumours (MESOPATH-IM@EC)
- sporadic and hereditary malignant endocrine tumours in adults (TENpath)

Although lymphomas are not really rare tumours, some forms in particular are only rarely seen in non-specialised laboratories, and are hence a problem for diagnosis and treatment management. Therefore, an additional anatomopathological reference network was dedicated to perform the double reading of all new lymphoma cases.

In 2010 the **double reading of anatomical pathological specimens** of rare cancers and lymphomas was initiated. In 2011, the 4 anatomopathological reference networks confirmed the diagnosis of 14 318 rare cancers and lymphomas through double reading;[10] the national annual incidence of the concerned pathologies was estimated to be between 16 000 and 18 000 new cases. For 1 634 cases, the double reading resulted in an altered treatment plan and for another 981 cases the diagnosis was adapted without any direct impact on the treatment plan.[10] In a lot of situations, additional molecular biological or immuno-histochemical tests were required and a tumour specimen was sent to a tumour bank.

More striking data were collected in the French Rhône-Alpes region, where the histological data of 448 patients diagnosed with sarcoma between March 2005 and February 2006 were re-assessed by an expert panel.[11] Full concordance was reported for only 54% of cases and more than 45% of first diagnoses were declared invalid by the expert panel conducting the centralized pathological review.

The following step will be a cost-effectiveness evaluation of the double reading to identify the more cost-effective indications of this process.

Appendix 5.1.3. Multidisciplinary treatment planning

Multidisciplinary treatment planning meetings have been organised by all expert centres at the regional, the interregional as well as at the national level, in addition to MDT meetings organized by centres of expertise themselves.[10] The regional MDT meetings represent the first expertise level whereas the national MDT meeting is a second expertise level, to resolve specific difficulties. These MDT meetings for referral, organized at a higher level, concern three potential situations: 1) all new patients diagnosed with a rare cancer in 2011; 2) patients diagnosed with a rare cancer several months or years ago, for whom the cancer progresses; this progression is an indication for discussion in a MDT meeting; 3) patients

who were already recorded in a centre of expertise for whom the cancer progresses.

These consultations are most often organised by web conference and hence accessible for other European experts. In this way, Belgian and Swiss centres participate in the consultations of TUTHYREF (an expert centre specialised in refractory cancer of the thyroid gland) in Villejuif. Other MDT meetings used interactive forums, with a description of a case sent by e-mail and discussed with all involved experts by phone.[10]

Appendix 5.1.4. Clinical guidelines

All experts involved in regional and national centres of expertise actively develop **clinical guidelines** for the management of patients with rare cancers. These guidelines are posted on dedicated websites (e.g. sporadic and hereditary malignant endocrine tumours on the website of RENATEN). In 2011, seven rare cancers had been covered by such guidelines.[10]

Appendix 5.1.5. Research

All national expert centres are involved in fundamental, translational or clinical **research** on rare cancers; various expert centre coordinators are also engaged in international research projects.[10] The impact of the rare cancer research engagements will be evaluated after 2 to 3 years. During the year 2011, 46 clinical trials have been initiated or were ongoing and 16 new trials were finalized for rare cancers. In parallel, 16 INCa Centres for Early Phase Clinical Trials (Centres Labellisés INCa de Phase Précoce, CLIP²) were designated in order to facilitate access to innovative treatments and their evaluation in early phase clinical trials. These structures facilitate the inclusion of patients in clinical trials with very short delays, also for patients with very rare cancers. In 2011, more than 800 patients with rare cancers were recruited in clinical trials. Other study designs (cohort studies, case-control studies, and post-market surveillance studies), sometimes more adapted to evaluate the effectiveness and the toxicity of new drugs, are also being conducted in France.

Appendix 5.1.6. Epidemiological surveillance

In the mean time, 13 of the 15 clinical networks have installed a national **database** containing incidence and follow-up data of more than 8 900 patients with rare cancers, which already resulted in an enhanced knowledge of these rare pathologies[10]. In addition, 3 expert centres also collaborate in international database initiatives.[10] Quality indicators are developed to compare results obtained by the centres of expertise (e.g. rate of surgical re-interventions for R1; delay between diagnosis and discussion in MDT meeting). An external audit will also assess the quality of medical data recorded.

Appendix 5.1.7. Training and information

With regard to **training and information**, all national expert centres organise medical schooling, scientific meetings and (inter)national conferences in the rare pathologies they are specialised in[10]. Besides, 10 expert centres have set up websites that diffuse up-to-date information to care providers, patients and all other interested, actually thanks to the involvement of patients organisations[10]. The majority of centres of expertise have a close link with these patient organisations, who are actively involved in the development of research protocols (patient information to obtain informed consent).

Two years after the set-up of the first expert centres for rare cancers in adults, the improvement for the patients are tangible:

- the double reading offers the confirmation of the diagnosis;
- the presentation and discussion of their case at the multidisciplinary treatment planning meetings enables an in-depth discussion of their case by experts, while their treatment can be taken care of by a local team; all coordinators have underlined the improvement of patient files discussed at the meetings;
- the network also moderates the set-up and organisation of clinical studies and improves the access to innovative treatments.

With regard to the professionals involved, one observes:

- a very close collaboration between the clinicians at the expert centres and the pathologists at the centres for anatomical pathology;
- a database for 13 of 15 pathologies concerned ;
- the elaboration of recommendations and national guidelines on different topics;
- a European or even international position for several rare cancer networks;
- a strong interaction between national expert centres and patient organisations for most structured pathologies.

Appendix 5.2. The Netherlands[z]

Appendix 5.2.1. Combination of national management and specialists' initiatives

In 2011, seven regional Comprehensive Cancer Centres (Integraal Kankercentrum, IKCs) have been fused into the Comprehensive Cancer Centre the Netherlands (Integraal Kankercentrum Nederland, IKNL) in order to combine national management with the important regional functions of the regional IKCs. IKNL is a knowledge and quality institute for health care providers in oncology and palliative care. In order to guarantee high quality care, IKNL looks at the content as well as at the organisational aspects of the care pathway. Over time, national associations of (medical) specialists in oncology (e.g. The Dutch Society for Radiotherapy and Oncology (Nederlandse Vereniging voor Radiotherapie en Oncologie, NVRO), the Dutch Society for Surgical Oncologists (Nederlandse Vereniging voor Chirurgische Oncologie, NVCO), the Professional Association for Care Professionals in Oncology (Beroepsvereniging van Zorgprofessionals Oncologie, V&VN Oncologie), the Dutch Society for Psychosocial Oncologists (Nederlandse Vereniging voor Psychosociale Oncologie, NVPO) and many national multidisciplinary tumour working groups in oncology were installed in order to develop more cohesive plans.

[z] The paragraphs on initiatives taken in the Netherlands were reviewed and approved by Sabine Siesling, Senior researcher, Comprehensive Cancer Centre The Netherlands (IKNL), the Netherlands.

Appendix 5.2.2. Quality of cancer care

Under the umbrella of the Signalling Committee of the Dutch Cancer Society (Signaleringscommissie Kanker, SCK) a 'Quality of Cancer Care' taskforce was set up in 2007, involving medical oncology specialists who had expertise in quality of care improvement projects.[12] The main responsibilities of this taskforce focused on the evaluation of the quality of cancer care in the Netherlands and the development of strategies for improvement. The experts first concentrated on the **relation between procedural volume and patient outcome**. Later, they tempted to identify **other factors** associated with high and low quality of the care provided in different regions and (types of) hospitals in the Netherlands. The question whether cancer care in the Netherlands could be organized differently to assure and possibly improve high quality of care for all patients, was the main subject of the investigation.[12]

Since the publication of the Dutch Health Council report of 1993 ('Kwaliteit en taakverdeling in de oncologie', quality and division of tasks in oncology), **national agreements** have been adopted on task allocation, concentration and spread of care with regard to a number of specialties and tumour types, including haematology, head and neck cancers, and bone and soft tissue tumours. Radiotherapeutic care and, to a lesser extent, pathology have always shown a certain amount of concentration in the Netherlands. For many other tumour types and complex diagnostic or therapeutic treatments, no national agreements have been made. At regional level, certain agreements exist between professionals on the referral of patients needing specific forms of care, as these need specific expertise and can therefore only be offered by a limited number of institutions.[13]

Variation in care outcomes was sometimes linked to hospital volume or hospital type, but the differences found between individual hospitals were much larger, even between comparable hospital types. In some instances, a high-volume hospital, a training hospital or an academic centre did not systematically guarantee higher care quality.[13] After all, it was noted that although several studies indicated that high-volume hospitals have lower mortality rates for a wide range of surgical procedures, the **primary mechanisms that mediate that effect are still not well understood**. Hollenbeck and co-workers observed that high-volume and low-volume

hospitals differ with respect to many processes of care before, during and after cystectomy for bladder cancer: among others high-volume hospitals had greater rates of pre-operative cardiac testing, intra-operative arterial monitoring, and use of a continent diversion.[14] On the other hand, the evaluated differences in the care pathways explained only 23% of the volume mortality effect. Patients treated at low-volume hospitals were 48% more likely to die in the post-operative period.

The Quality of Cancer Care taskforce of the Dutch Cancer Society recently proposed to concentrate specific cancer treatments in those hospitals that meet a set of criteria (http://www.kwfkankerbestrijding.nl). These criteria focus not only on procedural volume, but also on the available infrastructure, specialization of medical professionals, and outcome measures that should be reported by individual institutions. To include 'care outcomes' as essential criteria for concentration, it will be essential to make more data on differences in the cancer care process and on care outcomes available. Fundamental data on differences in case-mix between hospitals, reasons for deviation from guidelines, and the incidence of recurrence, for instance, are at present insufficiently disposable.

In 2010, the Dutch Cancer Society (Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding; http://www.kwfkankerbestrijding.nl) published the "Signalling report on the Quality of Cancer Care in the Netherlands" (Signaleringsrapport Kwaliteit van kankerzorg in Nederland), written by the Signalling Committee of the Dutch Cancer Society.[13] It illustrated the high variability in quality of cancer care between hospitals in the Netherlands. The report also contained recommendations to improve the quality of cancer care and to decrease the variability between hospitals.

At present, the Quality of Cancer Care working group of the Signalling Committee Cancer (SCK-werkgroep Kwaliteit van kankerzorg) is preparing a follow-up report that will comprise 2 parts:

- Field research: for thyroid cancer, prostate cancer, haematological malignancies and soft tissue tumours the variability in cancer care will be analyzed, in close collaboration with the Comprehensive Cancer Centre the Netherlands.
- Monitoring: in this part the developments in cancer care over the last two years will be mapped. For each cancer type decribed in the report of 2010 (i.e. breast, non-small cell lung, colorectal and bladder cancer), it will be evaluated which recommendations have been adopted, what the yield of the implementation was and which barriers were identified.

The report is expected early 2014. At the same time IKNL will publish a report on (differences in) patterns of care and outcome of 18 cancer types, among which some rare cancers like NETs, gliomas, oesophagus, pancreas and endometrium cancer. This report will be distributed together with the above mentioned report of the Signalling Committee of the KWF.

Appendix 5.2.3. Concentration of cancer care

The Dutch Society for Surgery described in 2011 a set of norms that surgeons as well as hospitals had to meet before certain surgical interventions could be undertaken. Based on this report, the Foundation of Oncological Collaboration (Stichting Oncologische Samenwerking, SONCOS, www.soncos.org) composed a multidisciplinary standardization report, in which also norms from medical oncologists, radiotherapists, gynaecologists, gastro-enterologists, pneumologists were adopted. The report describes for 21 cancer treatments in adults the criteria that a hospital has to fulfil in order to be able to treat the most common types of cancer; it is a living document that will be adapted on a yearly basis.[15]

The SONCOS norms reinforce the trend towards centralisation of care, especially for rare tumours and those cancers that need complex treatments. The Comprehensive Cancer Center the Netherlands (IKNL) evaluated the impact of those norms on the hospitals and the patients.[16] The impact on the hospitals (i.e. they have to refer the care of a certain cancer when they do not reach the introduced volume norm) is most pronounced for rare tumours.

Specialized clinical care (topklinische zorg) in the Netherlands is concentrated at the level of **eight university medical centres** (UMCs)[aa] and for some indications also in some **Collaborating Specialized Clinical Care Training Hospitals** (Samenwerkende Topklinische opleidingsZiekenhuizen, STZ). The STZ hospitals play an important task in the training of medical specialists and offer specific care (e.g. pancreas surgery). The UMCs treat so-called tertiary referral patients (topreferentie patienten), who are patients with rare and complex diseases who need highly specialized multidisciplinary treatment. The Dutch Federation of University Medical Centres (NFU) is developing a special web site to help patients and providers identify the appropriate reference centre for their disease (http://www.nfu.nl/trf/.). This type of care is financially supported by the government.

Appendix 5.2.4. Centralisation to specialized centres – some examples

Centralisation to specialised oncology centres has been advocated by national guidelines of the Dutch Society of Obstetrics and Gynaecology in 2000 for **vulvar carcinoma**, a rare tumour requiring technical surgical skills that are beyond the training for general gynaecologists in the Netherlands. A population-based study demonstrated that centralisation of care of patients with vulvar malignancies has been well adopted in the Eastern part of the Netherlands.[17] Only a minority (12 patients in 9 years in the whole region for a yearly incidence of 1–2 per 100 000 women) of patients with vulvar squamous cell carcinoma (SCC) was not referred to a specialised oncology centre after the implementation of the recommendation. Being treated in a specialised oncology centre was associated with better survival even after adjustment for age and stage. Patients being treated in a specialised oncology centre also benefited from less treatment-related morbidity like wound breakdown, cellulitis, lymphedema and erysipelas.[17]

Another rare cancer, **oesophageal cancer**, was also the target for centralisation in the Netherlands. Until 2007 approximately 350 oesophagectomies were performed annually in the Netherlands, shared by more than 50 different hospitals.[18] In 2006, a minimum volume of 10 oesophagectomies per year per hospital was enforced by the Dutch Healthcare Inspectorate (Inspectie voor de Gezondheidszorg, IGZ); a limit that was further restricted to 20 cases per year in 2011 by the Dutch Society of Surgery. Wouters and coworkers[19] conducted a study to analyze whether centralization of oesophageal cancer surgery truly improves clinical outcome in the Comprehensive Cancer Centre[bb] West region in The Netherlands. After centralization there was not only a reduction in hospital mortality (reduced to a third of the original value), but also in number and severity of adverse events. This was also reflected in a lower number of re-interventions and shorter length of stay.[19] Dikken et al. evaluated the impact of the introduction of a minimal volume standard on postoperative mortality and survival.[20] Between 1989 and 2009, the proportion of patients treated in high-volume hospitals increased for oesophagectomy, for which a standard was introduced in 2006, from 7% to 64%. In the same time span, the proportion of patients treated in high-volume hospitals for gastrectomy, for which no standard was introduced, decreased from 8% to 5%. For oesophagectomy, high hospital volume was significantly associated with lower 6-month mortality (decrease from 15% to 7%, hazard ratio: 0.48, $p<0.001$) and 3-year survival (from 41% to 52%, hazard ratio: 0.77, $p<0.001$). For gastrectomy there was also a positive trend in 6-month mortality (decrease from 15% to 10%) and 3-year survival (from 55% to 58%), but there was no significant association with hospital volume.[20]

[aa] Amsterdam: AMC; Amsterdam: VUmc; Leiden: LUMC; Utrecht: UMC Utrecht; Rotterdam: Erasmus MC; Groningen: UMCG; Nijmegen: UMC StRadboud; Maastricht: azM/Maastricht UMC+.

[bb] Comprehensive cancer centres (CCCs) are non-hospital organizations that serve as platforms for regional and national consultation between professionals.

Research conducted on volume-outcome for **bladder cancer** revealed that the more experienced treatment teams (including urologist, oncologist, radiotherapist and pathologist) on surgical intervention and/or the treatment of complications obtained the better the outcomes. As a consequence of these results, the Dutch Urological Association (Nederlandse Vereniging voor Urologie, NVU) decided that the treatment of muscle-invasive bladder cancer by means of bladder resection involving radical cystectomy and urine deviation must be discussed in multidisciplinary teams and must be carried out in hospitals possessing an adequate infrastructure and specially trained professionals. In the view of the working group, regionalisation and the safeguarding of quality through an audit system will lead to quality improvements, certainly if these hospitals are selected on the basis of their proven care outcomes. No unequivocal conclusions could be drawn for other cancers such as non-small cell lung cancer, colon cancer, rectal cancer and breast cancer.[13]

The main objective of the National Working group for Head and Neck Tumours (Nationale Werkgroep Hoofd- en Halstumoren, NWHHT) is the improvement of quality of care in **head and neck cancers**. One of the most important means to achieve this goal was centralisation of care.[13] The care of head and neck tumours has been recognised by the Minister of Health as "top referent care", which implies that it should be performed in a university hospital.[21] Minimum criteria for head and neck oncological centres have been listed in the Care Guide 2007.[13]

According to the "signalling report 2010", 90% of all patients with head and neck cancers were treated in NWHHT centres. The EUROCARE-3 project demonstrated that concentration of care resulted in better results: among all European countries, the Netherlands ranked first with respect to 5-years survival in patients with head and neck cancers.[22]

Each year, about 500 new **children** aged up to 18 years old are treated in one of the 7 centres for children oncology and stem cell transplantation. There is intensive cooperation between these centres within the Foundation for Paediatric Oncology in the Netherlands (Stichting Kinderoncologie Nederland, SKION) and also with centres and groups outside the Netherlands. Currently, a revision of the provision of oncologic care for children is considered to increase the centralization of care.[13]

More precisely, on the initiative of paediatric oncologists (http://www.skion.nl) and parents of children with cancer, paediatric oncological care will be centralised in 1 centre from 2016 on. The Prinses Máxima Centre for paediatric oncology will work along and together with 3 other paediatric hospitals (i.e. UMC Utrecht, Wilhelmina Kinderziekenhuis and Antoni van Leeuwenhoekziekenhuis) (http://www.prinsesmaximacentrum.nl/). Aim is to concentrate specialized care, research, education and training at the highest level. The less complex parts of the care pathway can then be performed in local shared care centres, under the supervision of the Prinses Máxima Centre.

In the Netherlands, families of (seriously) ill children can stay for a small charge in a Ronald McDonald house, which is situated in the neighbourhood or on the premises of the hospital where the child is being treated. Each of the 15 Ronald McDonald houses is run by one or two house-managers and a team of volunteers; funding is provided by donors.

Appendix 5.2.5. Quality improvement

A variety of instruments, such as guidelines, visitations and accreditations, data registration, and quality improvement projects is used by the involved parties (i.e. care professionals, professional associations, Comprehensive Cancer Centre the Netherlands (IKNL), the Health Care Inspectorate (IGZ), health insurance companies and patients' associations) to improve the quality of cancer care.

The Cancer Registration of the Netherlands (Nederlandse Kankerregistratie, NKR) is a **database** managed by the Comprehensive Cancer Centre the Netherlands (IKNL) and contains epidemiological, treatment and outcome data. The data are used to give **individual feedback to hospitals**: on a yearly basis, hospitals get an overview of the cancer incidence, number of surgeries and some tumour and patient characteristics. In 2013, the feedback was extended with 36 indicators that have been discussed with clinical experts and experts of IKNL. The information is illustrated with graphs, so that hospitals can easily see how they perform with regard to the national mean. The report also comprises recommendations how to improve their performance. Hospitals receive their individual feedback report, which is then further explained by an expert of IKNL (http://www.iknl.nl/nieuws/nieuws-detail/2013/10/18/ziekenhuisrapportages-met-nieuwe-indicatoren).

National, multidisciplinary, **evidence-based guidelines** currently exist for around 50 tumour types. These guidelines are developed by national multidisciplinary workgroups which include representatives of scientific associations and patients' organisations (www.iknl.nl).

Visitation programmes which focus on the functional evaluation of medical specialists are set up by almost all medical specialist associations. In addition, hospitals also have the option of commissioning a multidisciplinary visitation via the IKCs. This assesses the preconditions for good cancer care along the entire chain of cancer care provided in a hospital.

Unfortunately, the informal and confidential character of existing quality controls (visitations, audits and accreditations) remains a limitation. Failure to meet standards or observe agreements has only minor consequences, mainly because care professionals directly concerned are the only ones who are made aware of shortcomings and areas for improvement[13].

The Quality of Cancer Care taskforce further advocates **outcome registration and case-mix adjusted feedback** to individual hospitals because it was proven that mirror-information may act as a catalyst for quality improvement in care.[12] The Wouters et al. study on oesophageal cancer for instance, illustrated that timely feedback of results to individual hospitals and surgeons led to voluntarily changes in referral patterns in a time-span of 2-3 years.[19]

In 2009 the National Breast Cancer Consultation the Netherlands (Nationaal Borstkankeroverleg Nederland, NABON) initiated the development of a multidisciplinary set of quality indicators for the treatment of breast cancer. The indicators were elaborated by all concerned professional associations, the Breast Cancer association the Netherlands (Borstkankervereniging Nederland, BVN) and methodological experts of IKNL and the Dutch Institute for Clinical Auditing (DICA). Not all indicators have been validated yet; still they can already be used by hospitals for internal quality improvement. Since 2013, the external indicators can be forwarded to insurance companies and patients' associations, under the condition that the hospital has given its consent (http://werkgroepeniknl.nl/Landelijk/werkgroepen/nabon_openbaar/index.php?id=6580). With regard to rare cancers, clinical auditing is organised for upper GI cancer (http://duca.clinicalaudit.nl/), pancreas cancer (http://dpca.clinicalaudit.nl/), melanomas (http://dmtr.clinicalaudit.nl/) and hepatobiliary cancer (http://dhba.clinicalaudit.nl/).

Appendix 5.2.6. Information for patients

Patients in need for help, support or information are able to obtain this information via the website or telephone help line of the Dutch Cancer Society (Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding).[23] In addition, on the website "SIB op maat" (http://www.sibopmaat.nl; SIB stands for 'samenstellen informatie over bijwerkingen' – compose information on side effects) health care professionals as well as patients can find information on standard treatment plans, the side effects of oncological treatments and advice for patients.[23]

On the website https://www.kanker.nl/, cancer patients can find the links to patients' associations, to psychosocial support (offered in "inloophuizen"), tailor made information, discussion fora, personal stories, etc.

Appendix 5.3. UK/England[cc]

Appendix 5.3.1. Historical Background

The strategy by which the Government aimed to ensure high quality care for all cancer patients in England and Wales was outlined in the 1995 Calman–Hine report[24] and the subsequent NHS Cancer Plan.[25] These documents advocated a change from a generalist model of care (i.e. care given by general surgeons and physicians) to a fully specialist service, i.e. site specialists in each relevant discipline working together in multidisciplinary cancer teams.[26]

The 1995 Calman-Hine report[24] was the first comprehensive cancer report to be produced in the UK, and set out principles for cancer care and the clinical organisation for service delivery.

[cc] Despite several attempts, we did not succeed in getting any feedback from the English National Health Service on the content of the following paragraphs.

Three levels of care were proposed:

1. Primary care
2. Cancer Units in district general hospitals, designated to deal effectively with referrals from primary care and with the diagnosis, staging, and management of patients with common cancers.
3. Cancer Centres designated to provide expertise in the management of all cancers, including common cancers within their immediate geographical locality and less common cancers by referral from Cancer Units. Clear roles are defined for cancer centres, over and above the provision of radiotherapy services. These roles are centred on patients with intermediate frequency cancers and rare cancers or those who needed complex interventions. A small number of very rare cancers (e.g. choriocarcinoma) should be managed in a small number of Cancer Centres to ensure adequate specialisation.

Through a "top-down" decision approach, the hospitals were assigned one of the 3 categories and it was defined which care they were and were not allowed to deliver.[13]

The 2000 NHS Cancer Plan,[25] which was the first national cancer plan, took the Calman−Hine report as its starting point and extended its scope in many areas. It was a practical document that set out what needed to be done: it had numbers and costs. In particular, it attempted to deal systematically with shortfalls in manpower and facilities, set some clear objectives, identified resources, and adopted specific targets. These plans focused on waiting times and delays in access to diagnostic and treatment services.

The Calman–Hine report[24] as well as the NHS Cancer Plan[25] aimed to improve outcomes through the **reconfiguration of facilities and personnel**, rather than through the introduction of a new health technology; substantial resources have been invested in their implementation.[26] The model proposed that all patients with cancer were seen by specialists in their cancer type. These specialist surgeons or physicians were required to work closely with colleagues in multidisciplinary teams composed of diagnostic disciplines, surgical and non-surgical oncologists and nurse specialists. Thus, the policy sought a double transformation from patient access direct to specialists rather than generalists and from clinicians working individually to an overtly multidisciplinary model.[27]

The Calman−Hine report was followed by a policy framework with detailed policies and evidence-based guidance that covered services for specific types of cancer, starting with common cancers.[27] However, application of this policy within the National Health Service (NHS) was flawed and some important changes were **implemented inconsistently** (e.g. establishing cancer centres that were too small, not following guidance properly in service reconfiguration, constitution of multidisciplinary teams, role of key posts), perpetuating variations in service quality despite the report's aims.[27] Different reasons can be invoked. In particular, the human-resource consequences induced by the high specialisation and centralisation of care resulted in increased demand for trained site-specialists. A population-based study attempted to quantify the extent to which the Calman–Hine recommendations of multidisciplinary team formation and surgical site specialisation in colorectal cancer had been translated into practice by 2000, in the Yorkshire region of the UK.[26] The Calman–Hine recommendations were implemented at varying rates between 1995 and 2000. In some hospitals, teams were functioning according to some Calman–Hine principles from the outset; however, in no areas were all the recommendations fully realised by the end of the study period. Nevertheless, there was evidence to suggest that the move towards surgical site specialisation was associated with a greater use of preoperative radiotherapy and a more frequent application of an anterior resection in rectal cancer patients. Small statistically significant improvements were observed in five-year survival in relation to increasing adherence to the Manual of Cancer Service Standards, especially for colon cancer patients.[26]

Appendix 5.3.2. Cancer Networks and Reference Groups

In England, there are 28 NHS Cancer Networks that bring together the providers of cancer care (organisations that deliver cancer services to patients) and the commissioners of cancer care (organisations that plan, purchase and monitor cancer services) to work together to plan and deliver high quality cancer services for a specific population.[28] The NHS Cancer Networks aim to

- Improve cancer outcomes (e.g. increasing survival rates from cancers)
- Improve patient experience
- Improve the quality of treatment and care
- Improve access to appropriate high quality services

The Cancer Networks were chosen to reflect existing geographical patterns of referral and joint care for cancer patients, for example with regard to radiotherapy, specialised surgery or chemotherapy.[29] They cover populations varying between a half and 3 million people, and roughly follow local administrative boundaries. Network members are determined locally, drawing together managerial staff from NHS hospitals and clinical staff collaborating in tumour-specific multidisciplinary teams.[29] Based on the size of the population covered by a network, a minimum caseload was defined to maintain expertise and experience. For example, minimum population sizes were defined for colon cancer (200 000), upper gastro-intestinal cancer and rare head and neck tumours (1 million), and pancreatic cancer (2-4 million). Volume norms are also described in the clinical practice guidelines of NICE.[13]

In October 2012, the **NHS Commissioning Board (NHS CB)** was formally established; it has an overarching role in ensuring that the NHS delivers better outcomes for patients within its available resources.[30] From April 2013 on, the NHS CB is also responsible for the commissioning of all 'specialised' services. Strategic Clinical Networks and Operational Delivery Networks will be established to support the effective commissioning of services.

The NHS CB has agreed that Clinical Reference Groups will be extended and tasked with developing service specifications and policies to ensure compliance with the NICE Improving Outcomes Guidance for rare cancers. The focus will be on embedding service improvement changes for:[30]

- Brain & central nervous system (CNS) tumour pathways between centres and local services
- Haemato-oncology pathology arrangements
- Ensuring compliance with surgical requirements for sarcoma services
- Specialised surgery for hepato-pancreatic biliary cancers
- Specialised surgery arrangements for specified urological cancers
- Teenagers & Young Adult Cancer Pathways

Specialist cancer services are only commissioned if they are already compliant, or if they have demonstrable plans to be compliant within agreed timeframes with the NICE Improving Outcomes Guidance (IOG). For example, it is expected that providers are fully engaged in the national peer review process, and are working towards full compliance with the necessary specialist cancer standards.

All providers are expected to formally adopt, within their own clinical governance processes, the locally agreed pathways, policies and clinical guidelines in the Strategic Clinical Network to which they are affiliated. In addition, providers are required to provide seamless care across organisational boundaries, throughout the whole care pathway. Full engagement with the Cancer Network is seen as pivotal to the provision of specialist cancer services.[30]

Appendix 5.3.3. Initiatives for rare and complex cancers

In 2011, the Department of Health launched the national cancer plan "Improving outcomes: A strategy for cancer";[31] in this document two paragraphs were devoted to rare cancers:

- For GPs, spotting the signs and symptoms of rarer forms of cancer can be particularly challenging, as they may only see one or two instances of the cancer in question in their career. It is, however, clear that more needs to be done to raise awareness of the signs and symptoms of rarer cancers and to improve the pathway to diagnosis for people with rarer cancers. A recent survey by the Rarer Cancers Foundation of nearly 400 patients found that nearly one third of respondents had been reassured by their GP and not asked to return when they had first presented with symptoms. Perhaps unsurprisingly, a similar proportion of respondents rated their experience of the pre-diagnosis phase of their care as poor or very poor. Of those who responded to the survey, more than one quarter reported that their cancer was diagnosed at an advanced stage.
- Providing high quality decision aids and promoting early referral to secondary care will be central to our efforts to improve the diagnosis of rarer forms of cancer, as well as more common tumours. Through the National Awareness and Early Diagnosis Initiative (NAEDI), the Department of Health will also work with charities which represent patients with rarer forms of cancer to assess what more can be done to encourage appropriate referrals and earlier diagnosis of rarer cancers.

Appendix 5.3.4. Patients' associations

The **Rarer Cancers Foundation** is a national cancer charity that focuses on rare and less common cancers.[32] It "exists to ensure that people with rarer cancers have access to the best services and outcomes." More precisely,

- They provide up to date information on rarer cancers and treatment options available;
- They enable supportive networking for patients, carers and clinicians;
- They act as a gateway, directing patients to further avenues of support and information, such as patient groups or charities;
- They raise awareness about the less common cancers;
- They give a voice to 'forgotten' cancers;
- They produce information for both patients and healthcare professionals;
- They campaign for change at government level to secure the best possible patient journey for people living with rarer cancers.

The **Specialised Healthcare Alliance** (SHCA) is a coalition of 61 patient-related organisations supported by nine corporate members which campaigns on behalf of people with rare and complex medical conditions.[33] They organised a series of nine workshops focussing on quality and productivity in services including rare cancers, haemophilia, blood and marrow transplantation which fed into the report "Leaving No One Behind - Care for People with Rare and Complex Conditions", published in 2011.[34]

Appendix 5.3.5. Tumour tissue banks

In 2011, the **United Kingdom's** first **brain tumour tissue bank** was created, housed in Southern General Hospital in Glasgow, Scotland.[35] It will provide a large number of samples to researchers, with the goal of accelerating research toward treating this group of rare diseases. The new tissue bank, available to researchers from academia and industry, was made possible by funding from brain cancer charity Braintrust.

Appendix 5.4. Denmark[dd]

Appendix 5.4.1. Healthcare in Denmark

Denmark has a universal health care system, financed by taxes and not by social contributions. Since the structural reform in 2007 where Denmark moved from 13 counties to five regions, the Danish health care sector has three political and administrative levels: the state, the regions and the municipalities (national, regional and local levels). The health care service is organised in such a way that responsibility for services provided by the health service lies with the lowest possible administrative level. The idea is that services should be provided as close to the users as possible.

The health system is largely financed through municipal taxation with integrated funding and provision of health care at the regional level. Regions are not allowed to levy taxes, and the health service is primarily financed by a national health care contribution of 8 per cent combined with funds from both government and municipalities. Approximately, 9.8% of the GDP is being spent on healthcare.

At the national level, the Ministry of Health sets goals for the national health policy, provides health legislation including tasks for regions and municipalities, oversees the quality of care and initiate, coordinate and advise on health issues. The Ministry of Health works very closely with the Danish Health and Medicines Authority (in Danish: Sundhedsstyrelsen) which is the supreme authority in healthcare and regulatory control of medicine. This authority assists the Ministry and other authorities with professional consultancy on health issues and with a large number of administrative tasks including supervision and inspection of the health system, and the administration of the legislation related to medicines, pharmacists and medical devices.

For the five Danish regions, health care is the most important area of responsibility. The regions run the hospitals and are responsible for the primary practice sector.

Municipalities are responsible for home nursing, public health care, school health services, child dental treatment and prevention/rehabilitation.

Appendix 5.4.2. Organisation of cancer care

Since the late 1990's a heated public debate on cancer care in Denmark has been ongoing. This was mainly due to the fact that Denmark, in general, had higher cancer mortality rates than the countries it usually compares itself with, including Norway, Sweden and Finland. As a consequence, a large national steering committee was established in 1998 with a mandate that included (among other tasks) the development and implementation of evidence based diagnosis and treatment pathways for a number of cancer types (including a large number of cancers defined by RARECARE as rare), and to compare this evidence base with the existing situation in Denmark. Included in this work was an assessment of whether cancer care needed to be organised differently and whether there was sufficient competent personnel to deal with the various cancers. The steering committee had to provide recommendations for these domains per cancer type, taking cost and patient preferences into account and, subsequently, had to provide recommendations for implementation. Additionally, the committee was asked to assess whether there was a need for expanding this work to other cancer types.

The work of the steering committee lay the foundation for the three Danish Cancer Plans, which are comprehensive strategies aimed at improving cancer treatment in Denmark. While "Cancer Plan I" (released in February 2000) mainly focused on capacity building including training of personnel, the two subsequent strategies ("Cancer Plan II" from 2005 and "Cancer Plan III" from 2011) have been very focused on the patient perspective, including the establishment of rapid processes for diagnostics, a well-coordinated treatment pathway and high quality follow-up. The latest plan aims to evaluate whether recent years' strategic efforts have had an effect on lowering cancer mortality rates.[36]

The National Board of Health was given the task to facilitate the process of developing the national Cancer Patient Pathways (CPP). It had to design a process that ensured cooperation and involvement of all stakeholders. Politicians set the overall goal. Administrators contributed with organisational knowledge, health professionals with health specific

[dd] The paragraphs on initiatives taken in Denmark were reviewed and approved by Helene Probst, Chief Physician/Section Head of the Danish Health and Medicines Authority (Sundhedsstyrelsen), Denmark.

knowledge and politicians with the patient's voice and strong political power.[37]

Currently cancer care is centred around a set of standardised, integrated cancer pathways, developed by 14 working groups. The working groups consisted of representatives from all relevant medical societies including general practitioners, oncologists, pathologists and radiologists, together with specialists from the medical fields relevant to the specific cancer, the Danish Multidisciplinary Cancer Groups (DMCGs, who had a tradition of formulating clinical guidelines), nursing colleges and medical representatives from all five health regions.[37] The pathways, developed in 2007 and 2008, first implemented in 2009 and revised in 2011, are established to cover the full care continuum, starting from a reasonable suspicion of cancer, over diagnosis, treatment and up to follow-up. They all describe standard timeframes for the various elements involved in the pathway in order to avoid unnecessary delays. In 2012, there were 32 pathways for different cancer types, for common as well as for rare cancers (cfr. infra).[38]

While the initial suspicion of cancer usually takes place in the primary sector, the responsibility of diagnosis and treatment of cancer is anchored at hospital level. For each (rare) cancer type a hospital can have one of the following three designations;

- Main function (not assigned as a specialty function)
- Regional function (can be assigned to 1-3 hospitals in each of the 5 Danish regions)
- Highly specialised function (can be assigned to 1-3 hospitals in the entire country)

This approach of specialty planning has not only been installed for cancer, but for the entire specialised health service, as specialty planning is very important in the Danish health care system.

This split is made to ensure that not every hospital will try to take care of every cancer type. Thus, the designations are primarily based on the volume of each cancer type, e.g. main function hospitals only deal with common cancers including lung, breast and colorectal cancers, but also on complexity and resources. However, also the main function level hospitals have to prove that they qualify with regard to e.g. case load, accessibility, facilities, competences and collaboration with more specialized hospitals.[39]

Appendix 5.4.3. Organization and management of rare cancers

The treatment of rare cancers will, depending on the annual case load, complexity and resources needed for that particular cancer type, take place in regional function or in highly specialized function hospitals. The setting of requirements and designations (specialty planning) is ultimately the responsibility of the Danish Health and Medicines Authority. However, there is a large consultation process with stakeholder organisations including organisations representing the medical professions, the regions and the Ministry of Health that feeds into the establishment of requirements. The process is such that the Danish Health and Medicines Authority receives applications from hospitals who are candidates to manage a specific rare cancer type, and within this application process the hospital has to prove that it can ensure a care continuum including the management of surgery, and chemo and/or radiation therapy. The final placement of a hospital at a certain specialty level is based on an assessment of the rare cancer type with respect to complexity, frequency (case load) and use of resources. The specialty planning is revised (hospitals receives designations) every 3 years. Public as well as private hospitals can apply.[39]

To ensure the necessary experience and quality, a regional function hospital should see around 100 patients with a certain cancer type per year. This number can be a bit lower in cases where treatment is not very complex and/or where it is judged to be of added value for patients in that particular area to keep the function. Head and neck tumours, cancer in the ovaries and uterus and cancer in the brain are all examples of cancers that are dealt with at the regional function level hospitals.

For the highly specialized functions, dealing with very rare cancer types, the case load number aimed at per year is around 50 patients. But, even for these rare cancer types, there might still be up to 3 Danish hospitals assigned as highly specialized function hospitals to ensure a certain level of treatment proximity for the patient. In general, very complex treatments forms only take place within the highly specialized hospitals.

Appendix 5.4.4. Pathways for rare cancers

Denmark has established clinical pathways for the following rare cancers: lymphoma, tumours of the female genital system, head and neck, tumours of oesophagus and the stomach, tumours of pancreas and liver, tumours of (some types of) malignant skin tumours, tumours of the kidney, soft tissue sarcomas and GIST sarcomas / bone sarcomas, tumours of (some parts of) CNS, tumours of the male genital system, and melanoma of the uvea. For certain rare cancers (including tumours in the gallbladder, endocrine organs, neuroendocrine tumours, malignant mesothelium, familial adenomatous polyposis, tumours in peritoneum and cancer occurring during pregnancy) there are currently no established pathways.

Each pathway is divided into four main sections being:

- entrance into the pathway
- diagnostics
- initial treatment
- follow-up

There are several medical, logistic and communication actions required in each section of the pathway; responsibilities and timeframes are assigned to each step. For example, for a patient with suspected penis cancer the initial responsibility of whether or not to be assigned to the penis cancer pathway will be the responsibility of the general practitioner who takes care of referral to the pathway and afterwards the pathway will start.. This highly specialized referral centre will in this case have 6 calendar days to plan the diagnostic work up (second section) which has to be initiated no later than the 7th calendar day after referral. All diagnostic work up (journal writing, biopsies, biopsy analysis, multidisciplinary conferences, patient information etc.) has to be performed at the highly specialized centre within 21 calendar days. In the initial treatment period (third section) the penis cancer patient will be admitted to a highly specialized urologic department for the surgery; all decisions regarding further surgical treatment or adjuvant therapies will be taken by the multidisciplinary team at that department. If adjuvant treatment is needed this will be taken care of at an oncology department. A patient has a person assigned as a coordinator to ensure a smooth patient centred process. The highly specialized department also takes care of follow-up and control visits.[38]

APPENDIX 6. NAMES OF THE STAKEHOLDERS' REPRESENTATIVES

Surname	Name	Stakeholder
Yves	Benoit	UZ Gent
Michaël	Callens	Mutualités Chrétiennes
Jean-Jacques	Cassiman	Fund Rare Diseases and Orphan Drugs
Donald	Claeys	Collegium Chirurgicum Belgicum
Claudio	Colantoni	Cellule Stratégique Affaires Sociales et Santé Publique
Véronique	De Graeve	Zelfhulpgroep NET & MEN kanker
Ellen	De Wandeler	Centre du Cancer - KankerCentrum
Patrick	Galloo	Mutualités Socialistes
Geneviève	Haucotte	INAMI - RIZIV
Lore	Lapeire	UZ Gent
Lia	Le Roy	Werkgroep hersentumoren
Liesbeth	Lenaerts	Centre du Cancer - KankerCentrum
Johan	Pauwels	Zorgnet Vlaanderen
Marc	Peeters	College of Oncology
Ward	Rommel	Vlaamse Liga tegen Kanker
Karin	Rondia	Fondation contre le cancer
Betty	Ryckaert	Werkgroep hersentumoren
Anne	Uyttebroeck	UZ Leuven
Simon	Van Belle	College of Oncology (former president)
Saskia	Van den Bogaert	SPF/FOD Santé Publique
Marc	Van den Bulcke	Centre du Cancer - KankerCentrum
Robert	Van den Oever	Christelijke Mutualiteit
Liesbet	Van Eycken	Stichting KankerRegister
Wim	Waelput	UZ Brussel
Patrick	Waterbley	SPF/FOD Santé Publique

REFERENCES

1. Onkelinx L. National Cancer Plan 2008-2010. Brussels: 2008.
2. Van Hoof E, Remue E, Lenaerts L, De Wandeler E, Mores B, Goolaerts J. Evaluatie van het Kankerplan 2008-2010. Brussel: Wetenschappelijk Instituut Volksgezondheid, Kankercentrum; 2012.
3. Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. Policies for Rare diseases and Orphan Drugs. Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. Health Technology Assessment (HTA) KCE reports 112C (D/2009/10.273/32)
4. Gatta G, Van Der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: The rare cancer burden in Europe. European Journal of Cancer. 2011;47(17):2493-511.
5. Parisse-Brassens J. At the crossroads of two worlds: Rare Cancers [Web page].Paris: http://archive.eurordis.org/article.php3?id_article=1890;2008 [cited 16 May]. Available from: http://archive.eurordis.org/article.php3?id_article=1890
6. Fund Rare Diseases and Orphan Drugs. Recommendations and Proposed Measures for a Belgian Plan for Rare Diseases. Final Report. Brussels: King Baudouin Foundation; 2011.
7. Decision no. 1295/1999/EC of the European parliament and of the council of 29 April 1999 adopting a programme of community action on rare diseases within the framework for action in the field of public health (1999–2003), 1999. Available from: http://www.rzadkiechoroby.pl/dodatkigraf/UE%20Decision%201295_1999%20on%20rare.pdf
8. Rarecare. Available from: http://www.rarecare.eu/rarecancers/rarecancers.asp
9. Tejedor Del Real P, Sosa Iudicissa M. Proceedings of the Workshop ‘Rare Cancers: The added value of closer cooperation’. Brussels: European Parliament; 2011.
10. European Society of Pathology and Rare Cancers Europe. International Survey on Pathology in Rare Cancers - Summary Report [Web page].2012. Available from: http://www.rarecancerseurope.org/Surveys

11. Arbiser ZK, Folpe AL, Weiss SW. Consultative (expert) second opinions in soft tissue pathology. Analysis of problem-prone diagnostic situations. Am J Clin Pathol. 2001;116(4):473-6.
12. Orphanet. Lists of medicinal products for rare diseases in Europe. 2013. Orphanet Report Series, Orphan Drugs collection Available from: http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf
13. All EUROPLAN Partners. Recommendations for the development of national plans for rare diseases. Brussels: European Commission Public Health Program 2003-08; 2010. Health Information (HI 2007)
14. Greenlee RT, Goodman MT, Lynch CF, Platz CE, Havener LA, Howe HL. The occurrence of rare cancers in U.S. adults, 1995-2004. Public Health Rep. 2010;125(1):28-43.
15. Gatta G, van der Zwan JM, Siesling S, Otter R, Tavilla A, Mallone S, et al. Technical report with basic indicators for rare cancers and health care related macro indicators. 2010. Grant Agreement N° 2006113; Work Package N°5; Deliverable N°13
16. European Parliament. Proceedings of the workshop: 'Rare cancers: the added value of closer cooperation'. Brussels 2011. Available from: http://www.europarl.europa.eu/RegData/etudes/divers/envi/2011/464440/IPOL-ENVI_DV(2011)464440(PAR00)_EN.pdf
17. van Belle S. Behandeling van zeldzame tumoren in België. College voor Oncologie; 2009.
18. Wagstaff A. Europe's rare cancer community calls for a more radical approach. Cancer World. 2009.
19. Gatta G, Ciccolallo L, Kunkler I, Capocaccia R, Berrino F, Coleman MP, et al. Survival from rare cancer in adults: a population-based study. Lancet Oncol. 2006;7(2):132-40.
20. Wouters MWJM, Gooiker GA, Van Sandick JW, Tollenaar RAEM. The volume-outcome relation in the surgical treatment of esophageal cancer: A systematic review and meta-analysis. Cancer. 2012.
21. BlueCross BlueShield Association. Blue Distinction Centers for Complex and Rare Cancers, [Web page].2009. Available from: http://www.bcbs.com/why-bcbs/blue-distinction/
22. Statistics Belgium. Life tables for the year 1999-2008 [Web page]. [cited May 23, 2012]. Available from: http://statbel.fgov.be/fr/modules/publications/statistiques/population/table_de_mortalite_overview.jsp
23. Belgian Cancer Registry. Cancer Survival in Belgium. Brussels: 2012.
24. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol. 2007;8(9):773-83.
25. Awada A, Boogaerts M, Bosly A, Bron D, De Grève J, Dirix L, et al. Livre blanc: la prise en charge du cancer en Belgique - relever les défis de demain. Louvain: 2007.
26. Onkelinx L, Centre du Cancer. Plan Cancer - Etat des Lieux. Bruxelles: 2012.
27. Armstrong BK. The role of the cancer registry in cancer control. Cancer Causes Control 1992;3:569-79.
28. Fritz A et al. International Classification of Diseases for Oncology (ICD-O-3). WHO, editor. Geneva; 2000.
29. International Union Against Cancer. TNM Classifications of Malignant tumours. Sobin L, Gospodarowicz M, Wittekind C, editor.; 2009.
30. Belgian Cancer Registry. Cancer Incidence in Belgium, 2008. Brussels: 2011.
31. Belgian Cancer Registry. Cancer in children and adolescents. Brussels: 2013.
32. Vlayen J, Vrijens F, Beirens K, Stordeur S, Devriese S, Van Eycken E. Quality indicators in oncology: testis cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE Report 149.

33. Vlayen J, De Gendt C, Stordeur S, Schillemans V, Camberlin C, Vrijens F, et al. Quality indicators for the management of upper gastrointestinal cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCE Report 200.
34. Vlayen J, Stordeur S, Vrijens F, Van Eycken E. Quality indicators in oncology: prerequisites for the set–up of a quality system. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Report 152.
35. Raymaekers M, Bakkus M, Boone E, de Rijke B, El Housni H, Descheemaeker P, et al. Reflections and proposals to assure quality in molecular diagnostics. Acta Clin Belg. 2011;66(1):33-41.
36. Connolly JL, Schnitt SJ, Wang HH, et al. Role of the Surgical Pathologist in the Diagnosis and Management of the Cancer Patient. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. Hamilton (ON): BC Decker; 2003.
37. Ray-Coquard I, Montesco MC, Coindre JM, Dei Tos AP, Lurkin A, Ranchere-Vince D, et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions. Ann Oncol. 2012;23(9):2442-9.
38. Kim MS, Lee SY, Cho WH, Song WS, Koh JS, Lee JA, et al. Prognostic effects of doctor-associated diagnostic delays in osteosarcoma. Arch Orthop Trauma Surg. 2009;129(10):1421-5.
39. Lurkin A, Ducimetiere F, Vince DR, Decouvelaere AV, Cellier D, Gilly FN, et al. Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region. BMC Cancer. 2010;10:150.
40. Mittler MA, Walters BC, Stopa EG. Observer reliability in histological grading of astrocytoma stereotactic biopsies. J Neurosurg. 1996;85(6):1091-4.
41. Sharif MA, Hamdani SN. Second opinion and discrepancy in the diagnosis of soft tissue lesions at surgical pathology. Indian J Pathol Microbiol. 2010;53(3):460-4.
42. Harris M, Hartley AL, Blair V, Birch JM, Banerjee SS, Freemont AJ, et al. Sarcomas in north west England: I. Histopathological peer review. Br J Cancer. 1991;64(2):315-20.
43. Thway K, Fisher C. Histopathological diagnostic discrepancies in soft tissue tumours referred to a specialist centre. Sarcoma. 2009;2009:741975.
44. Bajetta E, Platania M. Pitfalls in neuroendocrine tumor diagnosis. Rare Tumors. 2009;1(2):e32.
45. European Observatory on Health Systems and Policies. Building European Reference Networks in Health Care - Exploring concepts and national practices in the European Union. Copenhagen: World Health Organisation; 2013.
46. SIOP Europe - The European Society for Paediatric Oncology. European Standards of Care for Children with Cancer. Warsaw: 2009.
47. National Institute for Health and Clinical Excellence. Improving Outcomes in Children and Young People with Cancer - The Manual. London: 2005.
48. International Agency for Research on Cancer. Breast Cancer Screening. In: WHO, editor. Handbook of Cancer Prevention. Lyon; 2002.
49. Coleman MP, Gatta G, Verdecchia A, Esteve J, Sant M, Storm H, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol. 2003;14 Suppl 5:v128-49.
50. Jassem J, Hall, Coombes, and International Collaborative Cancer Group (ICCG). Surgical approaches to early breast cancer in the Intergroup Exemestane Study: large differences by country and geographical region. In: Proceedings of 4th European Breast Cancer Conference; 2004.
51. European Parliament Resolution on Breast Cancer in the European Union, 18 March 2004.
52. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol. 2008;19(4):614-22.

53. Hulstaert F, Mertens A-S, Obyn C, Van Halewyck D, van der Straten B, Lievens Y. Innovative radiotherapy techniques : a multicentre time-driven activity-based costing study. Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCe Reports 198 (D/2013/10.273/9) Available from: https://kce.fgov.be/sites/default/files/page_documents/KCE_198C_Innovativeradiotherapy.pdf
54. FPS of Health Food Chain Safety and Environment, The Belgian Hadron Therapy Centre (BHTC) Foundation. Feasibility study of a Hadron Therapy Centre in Belgium. Brussels: 2013.
55. Vrijens F, De Gauquier K, Camberlin C. The volume of surgical interventions and its impact on the outcome: feasibility study based on Belgian data. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. KCE Report 113.C
56. Stordeur S, Vrijens F, Beirens K, Vlayen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast bancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE Report 150.
57. Belgian Cancer Registry. Rare Cancers in the Flemish Region. Brussels: 2013.
58. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med. 1979;301(25):1364-9.
59. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346(15):1128-37.
60. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349(22):2117-27.
61. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg. 2007;245(5):777-83.
62. Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. Eur J Cancer. 2012;48(7):1004-13.
63. van den Einden LC, Aben KK, Massuger LF, van Spronsen DJ, de Hullu JA. Successful centralisation of patients with vulvar carcinoma: a population-based study in the Netherlands. Eur J Cancer. 2012;48(13):1997-2003.
64. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, et al. Centralization of oesophageal cancer surgery: does it improve clinical outcome? Ann Surg Oncol. 2009;16(7):1789-98.
65. Morris E, Forman D, Haward B. The impact of the Calman-Hine report: analysis of breast and colorectal cancer surgical workloads and the degree of surgical site specialization in the Yorkshire region of the UK, 1990-2000. Eur J Cancer Care (Engl). 2007;16(2):150-5.
66. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev. 2012;3:CD005391.
67. Woo YL, Kyrgiou M, Bryant A, Everett T, Dickinson HO. Centralisation of services for gynaecological cancers - a Cochrane systematic review. Gynecol Oncol. 2012;126(2):286-90.
68. Vrijens F, Stordeur S, Beirens K, Devriese S, Van Eycken E, Vlayen J. Effect of hospital volume on processes of care and 5-year survival after breast cancer: a population-based study on 25000 women. Breast. 2012;21(3):261-6.
69. Vlayen J, Vrijens F, Devriese S, Beirens K, Van Eycken E, Stordeur S. Quality indicators for testicular cancer: a population-based study. Eur J Cancer. 2012;48(8):1133-40.
70. Dutch Institute for Clinical Auditing. DICA-Rapportages 2011 - Transparantie, keuzes en verbetering van zorg. Leiden: DICA Leids Universitair Medisch Centrum; 2012.

71. European Union Committee of Experts on Rare Diseases. Quality criteria for centres of expertise for rare diseases in member states. 2011. EUCERD recommendations Available from: http://www.eucerd.eu/?post_type=document&p=1224

72. European Union Committee of Experts on Rare Diseases. National centres of expertise for rare diseases & European collaboration between centres of expertise. 2011. EUCERD workshop report Available from: http://www.eucerd.eu/?post_type=document&p=1231

73. European Society for Medical Oncology. Improving rare cancer care in Europe. Recommendations on stakeholder actions and public policies. 2008. Available from: http://www.rarecancerseurope.org/IMG/pdf/ESMO_Rare_Cancers_RECOMMENDATIONS_FINAL.pdf