



Nationale Richtlijnen College voor Oncologie

A. Algemeen kader oncologisch kwaliteitshandboek

*B. Wetenschappelijke basis voor klinische paden voor diagnose
en behandeling colorectale kanker en testiskanker*

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A. algemeen kader oncologisch kwaliteitshandboek
B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker

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DISCLAIMER: Het is geenszins de bedoeling dat dit rapport letterlijk opgevolgd wordt of als standaard gebruikt wordt voor elke individuele patiënt. Een standaard is gebaseerd op alle beschikbare klinische gegevens en kan veranderen naargelang de wetenschappelijke kennis en technologie evolueren. Deze aanbevelingen dienen enkel als een richtlijn beschouwd te worden. Het navolgen van richtlijnen garandeert niet bij elke patiënt een succesvol resultaat. Bovendien mogen ze niet vooropgesteld worden als de enige handelwijze en andere aanvaardbare praktijken uitsluiten die hetzelfde resultaat nastreven. De uiteindelijke beslissing om een bepaalde klinische procedure te volgen ligt bij de zorgverstrekker, rekening houdend met de klinische gegevens van de patiënt en met de beschikbare diagnostische middelen en behandelmogelijkheden. Men mag verwachten dat deze aanbevelingen overgenomen en aangepast worden na lokale discussie in de eigen klinische staf of de daartoe bevoegde organen in het ziekenhuis.

Voorwoord

Kanker blijft doodsoorzaak nummer twee, onmiddellijk na hart- en vaatziekten. Een verouderende populatie gaat gepaard met een toegenomen kankerprevalentie. Tegelijkertijd is de oncologie er de afgelopen decennia dankzij veel research en een aantal nieuwe technologieën met rasse schreden op vooruit gegaan. Die twee met elkaar verzoenen vergt het herdenken van de organisatie van de zorg en het ontwikkelen van hulpmiddelen om die research evidence tot aan het bed te brengen van iedere kankerpatiënt in ieder ziekenhuis dat kankerzorg aanbiedt.

In België werd de ziekenhuisorganisatie van kankerzorg in 2003 ingrijpend geheroriënteerd met de invoering van de oncologische zorgprogramma's. Naast de nadruk op samenwerking en multidisciplinariteit, was één van de cruciale elementen de ontwikkeling van een oncologisch 'kwaliteitshandboek' met richtlijnen in elk zorgprogramma. Op nationaal niveau werd de coördinatie van de zorgprogramma's bij het College voor Oncologie in de schoot van de FOD Volksgezondheid gelegd. Op zich lijkt zo'n ondersteunende structuur voor kwaliteitsborging logisch. Denk maar aan de inspanning die anders elk individueel ziekenhuis moet leveren om zelf richtlijnen te gaan ontwikkelen of te kopiëren. In dat hele proces besloot het College dat het algemeen kader van zo'n kwaliteitshandboek en de basis voor die lokale richtlijnen of klinische paden best nationaal kan ontwikkeld worden. Elk zorgprogramma kan zich dan concentreren op de lokale vertaling en implementatie in eigen klinische paden.

Het College bestaat uit diverse disciplines en eminente experten en riep voor de ontwikkeling van haar eerste richtlijnen, over colorectale en testiskanker, de methodologische ondersteuning in van het KCE. Het voorliggend werk is op de eerste plaats de verdienste van de auteurs en meerdere experten zoals verder vermeld. Praktijkrichtlijnen vormen wereldwijd een belangrijk ondersteunend hulpmiddel bij het nemen van klinische beslissingen en oncologie kan moeilijk nog zonder. Oncologische richtlijnen zijn gradueel meer en meer gebaseerd op evidence van klinische research in de oncologie. De inbreng van experten is cruciaal in de grijze zones zoals diagnostiek waar vaak weinig studies beschikbaar zijn.

Richtlijnen vormen slecht één element in een kwaliteitssysteem. Een mogelijks nog belangrijker sluitstuk in de kwaliteitscirkel is de evaluatie van de resultaten in de individuele zorgprogramma's. Een eerste project in dat verband zit alvast in het jaarprogramma 2006 van het KCE en handelt over - opnieuw - de behandeling van colorectale kanker.

De ondersteuning van een College door het KCE was nieuw in zijn aard en we wensen dan ook onze welgemeende appreciatie uit te drukken voor de diverse experten die meestal in combinatie met een drukke dagtaak in patiëntenzorg en onderzoek, nog eens de tijd vonden om deze richtlijnen tot een goed einde te brengen. Het op til staande Europese CoCANCPG netwerk kan die vertaalslag door lokale experten en het aktueel houden van richtlijnen hopelijk nog vergemakkelijken.

Het ultieme doel van al deze initiatieven mag tot slot nog eens in de verf gezet, namelijk het verbeteren van de kwaliteit van de kankerzorg voor elke individuele patiënt. Geen loze slogan, maar een doelstelling waar het College en zeer velen op het terrein dagdagelijks hun schouders onder zetten.

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Samenvatting

Inleiding

In het Belgische gezondheidszorgbeleid werd de afgelopen jaren meer aandacht besteed aan de kwaliteit van zorgen en een meer efficiënte organisatie en samenwerking. Eén van de uitingen daarvan was de ontwikkeling van zogenaamde ‘zorgprogramma’s’ in een aantal gebieden, waaronder de oncologie. De Belgische wetgever heeft de nadruk gelegd op meerdere aspecten in de organisatie van de kankerzorg, zoals multidisciplinariteit, de coördinatie tussen de eerste lijn, het zorgprogramma voor oncologische basiszorg en het zorgprogramma voor oncologie. Om een dergelijk programma te beheren, is de beschikbaarheid van een multidisciplinair oncologisch kwaliteitshandboek noodzakelijk (KB 21.03.2003). Dit vermeldt het geheel van de structuren van het zorgprogramma, de gebruikte procedures en de organisatorische keuzes. Het College voor oncologie, gecreëerd om de kwaliteit van de zorgprogramma’s voor oncologie te bevorderen, heeft de missie om de ziekenhuizen te ondersteunen in de ontwikkeling van hun handboek ‘oncologie’ te ontwikkelen. Bij de uitvoering hiervan heeft het College beroep gedaan op de ondersteuning van het KCE om de bestaande wetenschappelijke literatuur en de buitenlandse ervaringen met betrekking tot dit concept te verkennen. Voor de ontwikkeling van de wetenschappelijke basis van de eerste richtlijnen bodde het KCE methodologische ondersteuning aan een specifieke werkgroep van het College. De eerste praktijkrichtlijnen gaan over colorectale kanker en testiskanker. Eerstgenoemde treft een groot deel van de bevolking. Testiskanker is veel zeldzamer, maar de kans op succesvolle behandeling is groot vooropgesteld dat de juiste zorgen correct worden toegediend. Als hulpmiddel voor de verspreiding van deze praktijkrichtlijnen werd een module ontwikkeld zodat ze via het internet kunnen geconsulteerd worden.

Het kwaliteitshandboek

Het kwaliteitshandboek omvat vooreerst een algemene voorstelling van het zorgprogramma: wie doet wat binnen het programma, welke zijn de gebruikte aanbevelingen en hoe verloopt de samenwerking met de overige zorgstructuren.

In de wetenschappelijke literatuur wordt er strikt genomen niets teruggevonden over de vorm of inhoud van een ‘kwaliteitshandboek’. Begrippen als protocol, praktijkrichtlijn, klinische pad, disease management, of case management hebben betrekking op deelaspecten van het handboekconcept.

Een protocol is een geheel van instructies die stap per stap moeten gevuld worden. Een praktijkrichtlijn is een instrument dat de clinicus ondersteunt in zijn medische besluitname omtrent een duidelijk bepaalde groep patiënten. Een klinische pad helpt de zorg voor een patiëntengroep lokaal te organiseren en in de tijd te plannen tenminste indien de betrokken procedures niet te variabel zijn. Disease management is eveneens op een groep patiënten of aandoening gericht, maar omvat daarbij elke mogelijke zorgverstrekking, van preventie over behandeling tot psychologische ondersteuning. Disease management gaat dus uit van een meer geïntegreerde aanpak dan een klinisch pad. Tot slot biedt case management een volledige zorgplanning die per patiënt wordt geïndividualiseerd.

In het buitenland bestaan er enkele voorbeelden, min of meer vergelijkbaar met het concept zorgprogramma. In de VSA, bestaan de CHOP (Community Hospital Oncology Program) of CCOP (Community Clinical Oncology Program). In Frankrijk is er een nationale coördinatie voorzien. In Andalusië kent men het gezondheidsplan voor oncologie.

Het CHOP-programma is een schriftelijke weergave van alle procedures en de ontwikkelde zorgstandaarden per niveau van zorgverstrekking (eerste lijn, ziekenhuis...). De CCOP-programma’s hebben als voornaamste doel de bevordering van de deelname

van oncologische centra aan klinische studies. Dit kan ook bijdragen aan de verspreiding op het terrein van een goede medische praktijk. In Frankrijk is er een netwerk van kankercentra (FNCLCC). De nationale coördinatie (INCA) van de oncologische interventies in Frankrijk tracht diverse elementen te kaderen in een multidisciplinaire context: praktijkrichtlijnenontwikkeling, kwaliteitsnormen en accreditering en geïndividualiseerde benaderingen van patientenzorg (sterk lijkend op klinische paden). Grosso modo ligt deze benadering deels in de lijn van het Koninklijk Besluit inzake zorgprogramma's voor oncologie in België.

Het Andalusische gezondheidsplan voor oncologie ten slotte, is per type kanker opgesteld en verwijst naar te gebruiken praktijkrichtlijnen en vermeldt ook expliciet organisatorische aspecten en zorgnormen.

Deze instrumenten bevatten meerdere kenmerken van een oncologisch kwaliteitshandboek, maar behelzen, strikt genomen, geen van allen het geheel van aspecten dat de Belgische wetgever met het kwaliteitshandboek beoogt. Het Belgische kwaliteitshandboek is dus een innovatief concept dat zijn voorgaande vindt noch in de literatuur noch in buitenlandse voorbeelden.

De hierboven aangehaalde voorbeelden, laten wel toe om de algemene structuur voor het kwaliteitshandboek te omschrijven. Dit kader wordt als template voor alle zorgprogramma's voor oncologie voorgesteld door het College voor oncologie. De diverse onderdelen van de template dienen dan lokaal, voor zover nog niet bestaande, nader ingevuld te worden met specifieke procedures, organisatorische keuzes, rekening houdende met de dagelijkse realiteit eigen aan elk zorgprogramma. De voorgestelde structuur omhelst de volgende aspecten:

- De lijst met de beschikbare infrastructuur, de diensten en het beschikbaar personeel
- De ontwikkelingmethodologie van het kwaliteitshandboek
- De algemene strategie van het zorgprogramma (missie, doelstellingen, kwaliteitsbeleid,...)
- De algemene klinische benadering (inhoud van het patientendossier, behandelingsplan, communicatie naar de patiënt toe...)
- De specifieke klinische benadering per soort kanker (praktijkrichtlijnen)
- Transversale thema's zoals psychosociale ondersteuning, voedingsrichtlijnen, deelname aan klinische studies ...)
- Specifieke benadering per specialisme (anatomopathologie, medische beeldvorming, radiotherapie, chirurgie ...)
- Algemene organisatie (multi- en interdisciplinaire samenwerking, communicatiebeleid, relatie met andere oncologische zorgstructuren, communicatie naar het Kankerregister ...)
- Beschrijving van de procedure voor updating van het handboek en de voorziene frequentie van deze updates.

Wetenschappelijke basis voor praktijkrichtlijnen

Praktijkrichtlijnen vertegenwoordigen een van de onderdelen van het multidisciplinair oncologisch handboek. Vanuit praktijkrichtlijnen kunnen in tweede instantie lokale klinische paden ontwikkeld worden en is het mogelijk om er kwaliteitsindicatoren van af te leiden.

Een belangrijke doelstelling daarbij is de vermindering van onverklaarbare zorgvariabiliteit op het vlak van zowel diagnose en behandeling als follow-up. Optimale kwaliteitszorg is zoveel mogelijk evidence-based.

Praktijkrichtlijnen voorgesteld door het College voor oncologie dienen als basisaanbevelingen beschouwd te worden en nog lokaal door elk zorgprogramma vertaald te worden in haar eigen aanbevelingen of klinische paden. Dit is vermoedelijk meest relevant voor interventies met weinig of geen bewijskracht. De doelgroep is op de eerste plaats de ziekenhuisartsen die in de zorgprogramma's voor oncologie betrokken zijn. Nochtans zullen ook huisartsen en de andere zorgverleners er zeker nuttige informatie terugvinden.

De ontwikkeling van praktijkrichtlijnen volgt een strikte methodologie die begint met een literatuuronderzoek en inventaris van bestaande praktijkrichtlijnen gevolgd door een kritische analyse.. In de ontwikkeling van evidence-based aanbevelingen vindt vervolgens een aanpassing plaats naar de specifieke Belgische situatie. In functie van de kwaliteit van de klinische studies die een aanbeveling ondersteunen, konden vervolgens zogenaamde 'grades of recommendation' ingevuld worden. Wetenschappelijke experten van diverse disciplines en betrokken wetenschappelijke verenigingen gaven hun input en uiteindelijk vond er nog een methodologische externe validatie plaats.

Praktijkrichtlijn colorectale kanker

De klinische vragen die aan de basis liggen van de ontwikkeling van deze richtlijnen zijn als volgt:

Voor alle patiënten met colorectale kanker lijden, onafhankelijk van geslacht of leeftijd,

1. Wat zegt de beschikbare wetenschappelijke evidence over diagnosestelling van colorectale kanker? Zijn er verschillende opties?
2. Wat zegt de beschikbare wetenschappelijke evidence over de behandeling van colorectale kanker? Zijn er verschillende opties?
3. Wat zegt de beschikbare wetenschappelijke evidence over de opvolging van patiënten met colorectale kanker?

De literatuur werd gezocht via Pubmed, Dare en via National Guidelines Clearinghouse. Vervolgens werd gezocht via de websites van de voornaamste agentschappen die praktijkrichtlijnen ontwikkelen. Een eerste selectie werd uitgevoerd op basis van het onderwerp (diagnose, behandeling of follow-up) en op basis van het al dan niet aanwezig zijn van een wetenschappelijk onderbouwde methodologie. Vervolgens werden de weerhouden praktijkrichtlijnen door twee experts van het KCE met behulp van het AGREE-instrument geëvalueerd. In geval van meningsverschil over een item werd een oplossing gezocht door onderling overleg tussen de experts.

Van de 19 praktijkrichtlijnen die gevonden werden, werden er 11 geëvalueerd als "sterk aanbevolen", 6 als "aanbevolen onder voorbehoud" en 2 als "niet aanbevolen" (gezien ze louter gebaseerd waren op consensus). Een synthese van de graad van aanbeveling van de verschillende praktijkrichtlijnen werd uitgevoerd, zodat een systeem met 3 niveau's van bewijskracht kon gebruikt worden:

- niveau A: evidence van goede RCTs of meta-analyses, of systematic reviews van RCTs;

- niveau B: evidence afkomstig uit gecontroleerde maar niet gerandomiseerde studies of uit observationele studies;
- niveau C: evidence van expertenconsensus, case-reports of case-series.

Als basis voor de Belgische praktijkrichtlijn werden vooral de praktijkrichtlijnen die als "sterk aanbevolen" werden geëvalueerd weerhouden, soms aangevuld met elementen van praktijkrichtlijnen die "onder voorbehoud" werden aanbevolen.

De details van de richtlijn zijn terug te vinden in het uitgebreide scientific report, volgend op deze samenvatting. U kan de algemene algoritmes voor de diagnose en behandeling van colon- en rectumkanker terugvinden op respectievelijk p. 19 en 29.

Praktijkrichtlijn testiskanker

De klinische vragen die aan de basis liggen van de ontwikkeling van deze Praktijkrichtlijnen zijn als volgt:

Voor alle patiënten die aan testis kanker lijden,

1. Wat zegt de beschikbare wetenschappelijke evidence over diagnostering van testiskanker? Zijn er verschillende opties?
2. Wat zegt de beschikbare wetenschappelijke evidence over de behandeling van testiskanker? Zijn er verschillende opties?
3. Wat zegt de beschikbare wetenschappelijke evidence over de opvolging van patiënten met testiskanker?

De gebruikte methodologie is identiek aan die van colorectale kanker, met uitzondering van de in de zoekstrategie gebruikte woorden. De selectie - en exclusiecriteria zijn gelijksoortig.

Er werden 9 praktijkrichtlijnen gevonden, waarvan 1 "sterk aanbevolen", 7 "aanbevolen onder voorbehoud" en 1 "niet aanbevolen". Een synthese van de gradaties werd uitgevoerd, zoals dit eveneens voor colorectale kanker gebeurde, en de praktijkrichtlijnen die geëvalueerd werd als "sterk aanbevolen" was de basis voor het ontwikkelen van de Belgische aanbevelingen. De validatie werd eveneens op dezelfde wijze uitgevoerd als voor de praktijkrichtlijn colorectale kanker.

De details van de richtlijn zijn terug te vinden in het uitgebreide scientific report, volgend op deze samenvatting. U kan het algemene algoritme voor de diagnose en behandeling van testiskanker terugvinden op p. 39.

Automatisering van guidelines

De verspreiding van praktijkrichtlijnen is een belangrijk en noodzakelijk gebeuren om de kans op succesvolle implementatie te vergroten. Specifiek hiertoe werd er een internettoepassing ontwikkeld die het moet mogelijk maken om op een eenvoudige manier de inhoud van een richtlijn te consulteren. Eerste voorbeeld betreft colorectale kanker. Eén van de eisen die vanuit het KCE aan dit systeem werd opgelegd is dat naar de toekomst toe andere praktijkrichtlijnen vlot kunnen toegevoegd worden of vervangen door geupdate richtlijnen. De basis voor het handboek i.e. met progressief meer en meer ontwikkelde richtlijnen zal via een website van het College voor oncologie toegankelijk zijn. De ontwikkeling van de internettoepassing gebeurde in twee fases: vooreerst de implementatie van een "step by step"-instrument dat de gebruiker toelaat om het traject van de patiënt te volgen in functie van zijn toestand, en vervolgens, een grafische voorstelling die de gebruiker toelaat om onmiddellijk naar het gewenste onderdeel in diagnose, behandeling of opvolging te klikken. Het project werd door het College voor oncologie gevalideerd. De installatie van de toepassing wordt verwezenlijkt door de FOD Volksgezondheid.

Conclusies en aanbevelingen

Dit project van het College voor oncologie van de FOD Volksgezondheid in samenwerking met het KCE heeft geleid tot een voorstel van structuur voor het multidisciplinair oncologisch kwaliteitshandboek waarvan ieder zorgprogramma's voor oncologie kan gebruiken. Daarnaast heeft het ook geleid tot de ontwikkeling van twee praktijkrichtlijnen (colorectale kanker en testiskanker). De daarbij gehanteerde methodologie waarbij meerdere overwegend internationale oncologische praktijkrichtlijnen aan de Belgische situatie werden aangepast heeft daarbij zijn vuurdoop ontvangen. Deze manier van werken is niet nieuw. Er zijn ondertussen meerdere internationale projecten om dit soort werk te structureren, zoals bijvoorbeeld in het kader van ADAPTE gebeurde (een ‘stepwise approach’ tot ‘transcontextual’ aanpassingen).

Er wordt eveneens een internettoepassing opgestart na openbaarmaking van dit rapport om de gebruiksvriendelijke toegang tot praktijkrichtlijnen te vergemakkelijken. Een wezenlijk onderdeel van een kwaliteitssysteem ontbreekt nog. De praktijkrichtlijnen dienen nog omgezet te worden in klinische paden en in bruikbare kwaliteitsindicatoren die het College van oncologie toelaten om haar missie te vervullen. Wat rectumkanker betreft zullen deze elementen in ieder geval een deel uitmaken van een reeds voor 2006 voorzien project van het KCE.

Tot besluit kunnen een reeks beleidsaanbevelingen voor de toekomst geformuleerd worden:

- Het volstaat niet om praktijkrichtlijnen te ontwikkelen. Men moet ze ook verspreiden en hun gebruik aanmoedigen. Zo kan de vertaling van praktijkrichtlijnen in kwaliteitsindicatoren en in klinische paden voor de zorgprogramma's voor oncologie een stimulans vormen. Het College voor oncologie beschikt in dit verband over een belangrijk initiatiefrecht. Het beschikbaar stellen van praktijkrichtlijnen op het internet is eveneens een belangrijk hulpmiddel voor hun verspreiding. Bovendien is het belangrijk om bij studies betreffende het uitvoeren van praktijkrichtlijnen zoals die door het KCE geleid, oplettend te blijven toezien of de aanbevelingen m.n. ook in de oncologie in de praktijk worden toegepast.
- Goed ontwikkelde en op het terrein verspreide praktijkrichtlijnen zullen evenwel niet noodzakelijkerwijs ook goed gebruikt worden. Het is dus belangrijk om hun implementatie te evalueren. Hier toe moet naar de artsen die bij de oncologische zorg betrokken zijn geluisterd worden om de sterktes en zwaktes van de praktijkrichtlijnen te analyseren, zowel wat hun inhoud (interne samenhang) als wat hun afstemming op de specifieke omgeving van de zorgprogramma's voor oncologie betreft. Anders gezegd: zijn ze bruikbaar in de dagelijkse praktijk? Natuurlijk zal ook de vertaling van praktijkrichtlijnen in kwaliteitsindicatoren het mogelijk maken om hun gebruik te evalueren.
- Ten slotte is het belangrijk om de structuur van geproduceerde praktijkrichtlijnen te standaardiseren, zodat de gebruiker vertrouwt geraakt met de voorstellingswijze, ongeacht het oncologische ziektebeeld. Het is daarbij van belang dat iemand hierin een coördinerende rol op zich neemt. Het College voor oncologie is zonder enige twijfel hiertoe de best geplaatste acteur op het veld.
- In de oncologie wordt er voortdurend wetenschappelijke vooruitgang gemaakt. Deze wetenschappelijke basis zal dan ook regelmatig geupdate moeten worden zodra er belangrijke nieuwe evidence beschikbaar is. Dit is bijvoorbeeld specifiek voor chemotherapie voorzien in de missie van het College.

Scientific summary

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I INTRODUCTION

The Belgian Health Authorities have set up various healthcare programmes in order to give coherence to the healthcare system. The first healthcare programmes were developed for cardiology and in vitro fertilization. Then the oncology healthcare programme was created. In parallel, various College of physicians charged to measure and promote quality in their respective setting have been organised.

Within the framework of the healthcare programme in oncology, the College of physicians for oncology has been charged through the Royal Decree of 21/03/03 [1] settling the norms for the healthcare programme in oncology :

- to elaborate a model of quality handbook
- to settle the indicators to register
- to perform quality audits
- to compare the quality handbooks of the various healthcare programmes in oncology
- to elaborate recommendations for oncologists skills assessment
- to elaborate recommendations on minimal activity volume for the healthcare programme

In order to support the College of physicians for oncology, the KCE has been asked:

- to search all information concerning the utilization of quality handbook in the scientific literature and abroad: does it exist and if so, what is the format, the content and how is it used ?
- to propose a general structure of a quality handbook, based on the evidence found.
- to give a scientific support to the College in writing National Cancer guidelines for several tumours and specially with the objective of developing clinical pathways, and in a further step quality indicators.
- to develop and edit on the internet an electronic version of the first guideline, making possible an easy development of electronic version of further guidelines

The present work has three parts. The first one is a synthesis of the international literature on quality handbook and all other concepts which could be used fully or partly as quality handbook. Several concepts as protocols, guidelines, clinical pathways...will be reviewed.

The second part, based on the literature review, presents the structure of a National quality handbook. It is only a structure and every healthcare programme in oncology is supposed to fill in the various drawers with its own material, depending on its specificities.

The third part contains the 2 first guidelines developed with the help of the KCE: colorectal cancer and testicular cancer. Other guidelines developed by the College of physicians in oncology have been reviewed (NSCLC, melanoma). They will not be presented here to not make this report too heavy.

Finally, the last part presents the development of an electronic web-based version of the colorectal cancer guideline.

2 MULTIDISCIPLINARY HANDBOOK IN ONCOLOGY

2.1 INTRODUCTION

The multidisciplinary handbook in oncology prescribed by the Royal Decree on the healthcare programme for oncology[1] is an innovation. There is nothing strictly equivalent as attested by the scientific literature and a search for similar concepts abroad. However, various existing models partially approach the concept of multidisciplinary handbook. Before extracting the interesting elements from them in order to build the structure of the handbook, it is important to precise some definitions because a quality handbook is neither a clinical guideline nor a clinical pathway. Then, the review of the literature will be presented and finally, a structure of multidisciplinary handbook in oncology will be built up, based on the most similar experiences found in the scientific literature and abroad. This structure will also be used to build a grid for reviewing the existing handbooks in the various Belgian oncology healthcare programmes.

2.2 DEFINITIONS

To reduce the unjustified variations of healthcare, and thus to improve their quality, several models of healthcare organization have been developed. Among those, it is necessary to quote protocols, the clinical practice guidelines, critical (or clinical, or integrated care) pathways, case-management, disease management and standards of care. The protocols are "step by step" instructions, intended to make sure that a task is carried out in a uniform way. The clinical practice guidelines are tools of clinical decision-making. The critical pathways and the disease management form part of what can be described as methodologies to structure the care. They are all tools formalizing sets of care procedures applying to the majority of the patients. They make it possible to better foresee the process of care and thus to plan it [2].

The case-management is a completely individualized approach corresponding to the plan of care.

Finally the standards of care are rules to be respected. They include guidelines and critical pathways. They represent the basis on which indicators to assess the quality of care are built.

2.2.1 Protocols

A protocol is a rigid set of instructions which has the purpose to describe the procedures to be followed within the framework of a patient's specific care-process (either for prevention, for diagnosis, for treatment, for follow-up...). Little or even no flexibility or variation is allowed [3]. A protocol describes the way in which a procedure should always be carried out and thus ensures a uniformity of the practices. It is used within the framework of clinical research (protocol of clinical trial for example), to allow the delegation of responsibilities, to define a clear demarcation between responsibilities, for teaching, to avoid omissions in case of not frequent, complex, high-risk situations[4].

2.2.2 Guidelines (guides de bonne pratique, richtlijnen)

The clinical practice guidelines reduce unacceptable or undesirable variations in practice and provide a focus for discussion among health professionals and patients. They enable professionals from different disciplines to come to an agreement about treatment and devise a quality framework, against which practice can be measured[3]. They are defined as documents developed in a systematic way to assist the expert or the patient in the decision-making about the suitable care for specific clinical circumstances. The goal of the guidelines is to improve the clinical decision-making[5].

2.2.3 Critical (clinical, integrated care) pathways (klinische zorgpaden, itinéraires cliniques)

In a systematic review of the literature since 1966 concerning the impact of Clinical Practice Guidelines on the improvement of the procedures and results of the treatments in oncology [6], the clinical pathways are defined in the following way: they are programmes more detailed than the guidelines determining not only the care to deliver but also their sequence and the responsibilities for every carer; the most used clinical pathways are very specific with a clear definition of who does what, to whom and on what time. The care pathways determine locally agreed multidisciplinary practice, based on guidelines and evidence where available, for a specific patient/client group[3].

Other documents insist on anticipation and time management linked with the clinical pathway, on their utility in term of reduction of the not justified variations and on their role to facilitate the introduction of the guidelines[7]. Finally, they provide an operational model making it possible to connect a result to a certain structure and to the used procedures [8].

2.2.4 Disease management

The disease management is an approach of the patients' care that stresses the coordination of the resources and a global and integrated solution of care during the whole course of the disease and the process of care. The costs are emphasized, since the goal of the disease management, developed in the context of the managed care in the USA, is to offer best quality to lower cost. The disease management includes case-management, use of guidelines, measurement of results, improvement of quality as well as programmes for prevention and wellbeing [9]. However, in oncology, it should be kept in mind that the type of tumour and the stage of evolution of the disease largely influence the multiple elements of a disease management programme.

2.2.5 Case management

It is a procedure by which a case manager writes down a treatment plan and the availability of services, in-house or external, for an individual patient. Then, it determines the needs for the patient as well as the resources necessary for the treatment, in agreement with the attending practitioner [2].

2.2.6 Standards and ISO standards:

The standards of care are rules from which it is possible to build up quality indicators [10]. They are tools to assist the clinician to deliver optimal care. The standards include the guidelines, the protocols and the clinical pathways [11]. For the Commission on Cancer, in the USA, the standards of care must cover 4 great fields: the multidisciplinary committee for oncology, oncology meeting, the results evaluation and quality improvement, as well as cancer registering. The standards are useful within the framework of an accreditation procedure. Quality evaluation, based on ISO

9001 standards [12] also consists in writing all the procedures in a handbook and, based on these procedures, to build the decisional trees (Write what you do – do as you write - demonstrate that you do what you have promised) [13]. In that sense, this practice basically does not differ from the accreditation on the basis of standards [14, 15]. However, the quality handbook of ISO system includes the whole set of procedures, the instructions of use, the guidelines, the whole set of documents linked with the quality policy of the institution or service [16].

Synthesis of the definitions: The various tools are presented in a table below according to their nature, to the target public and their principal objective:

	Nature	Public concerned	principal Objective	Remarks
Protocol	Set of instructions of the type "step by step"	A group of patients clearly definite and specific	To warrant the uniform realization of a task	Allows in particular the delegation of the tasks
Guideline	Tool of clinical decision-making	A group of patients clearly defined and specific	To reduce the not justified variations of the care	Developed on the basis of the EBM
Clinical Pathways	Tool for planning care at the patient level	the majority of the patients (at least $\pm 1\Sigma$) using a service or a procedure	To reduce the not justified variations of care	Use of the guidelines
Disease Management	Tool for planning care at the patient level and covering as well prevention, diagnosis, treatment as psychological aspects and patients comfort	the majority of the patients (at least $\pm 1\Sigma$) suffering from a given pathology	To reduce the not justified variations of care and to control the costs	- Use of the guidelines, the clinical pathways, the case management - In addition they also incorporate the quality policy
Case Management	Tool for planning care at the individual patient level	Each individual patient (within the framework of a definite service)	To improve quality of care	
Standards /ISO	Normes allowing the development of quality indicators which themselves allow the evaluation of the quality	Can relate to a particular service as well, a defined group of patients, all the patients, the whole of the hospital even the whole of a health system	To assess and to improve quality	Can include the guidelines, the clinical pathways, the disease management

2.3 LITERATURE REVIEW

Before reviewing the literature, it is important to bear in mind a clear definition of the multidisciplinary quality handbook. In the appendices of the Royal decree of 21 March 2003 setting the norms for the healthcare programme in oncology[1], the quality handbook includes the directives relating to the diagnosis and staging, the treatment and follow-up of patients, all the agreements concluded with other institutions from which or to which patients could be referred and the identity of the people working in the healthcare programme with indication of their respective tasks.

The Royal decree itself[1] defines the handbook in the following way: "Any hospital equipped with a basic healthcare programme in oncology must use a multidisciplinary oncology handbook, which:

- includes the multidisciplinary guidelines built up to fix diagnosis, treatment and follow-up of patients suffering from cancer, and also the organisational agreements relating to patients reference
- points all the specialists involved in oncology care dispensation, as well as their speciality and expertise
- points all the other staff members responsible for any tasks within the framework of the healthcare programme.

Moreover, the handbook must be evaluated at regular time intervals and possibly adapted according to the progress of science. The handbook can be consulted at the hospital by every doctor, every nurse and other healthcare professionals, including the general practitioners. For any patient suffering from cancer, a treatment plan is elaborated in accordance with the multidisciplinary directives of the oncology handbook. If the recommendations of the handbook are not followed, the plan of treatment must be the subject of a multidisciplinary oncology consultation....

The handbook must include

- the guidelines for diagnosis, treatment and follow up,
- all organisational aspects like the agreements with other structures, the multidisciplinary oncology consultation when the guidelines are not followed,
- the list of personnel and,
- the procedures in use to build up and update the handbook.

The handbook is thus not the simple juxtaposition of the different guidelines, but it defines in a coherent and coordinated way all the procedures based on the guidelines, namely the healthcare programme in oncology.

On the basis of text of the Royal Decree, the literature (Pubmed, base plate, CINHAL, SUMSearch) and Internet (<http://www.journalservice.com/Main.asp>, <http://search.kumc.edu/>, <http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi>, google) were explored with the following key words, possibly in association: - Oncology, cancer, neoplasms AND - quality manual - quality handbook - procedures - standards - clinical/ critical pathways - organization/management - guidelines - disease management - outcomes management - program - understanding program - quality evaluation - health services research - quality of healthcare - quality insurance.

Thereafter, certain more specific key words were used: CHOP (Community Hospital Oncology Program), CCOC (Community Clinical Oncology Program), ISO 9001

The different concepts found in the literature are briefly presented hereunder.

- I. Guidelines Clinical, critical pathways, Disease management, case management Standards and ISO 9001 which have already been presented

2. CHOP and CCOP (USA)

4. Network, coordination and oncology plans

CHOP and CCOP: The concept of CHOP is not new. At the beginning of the years 1980, this initiative is launched in the USA to improve the diffusion of the guidelines developed locally. The matters treated by these CHOP were primarily: staging, medical management, nursing and rehabilitation, community practice for breast, rectal and small-cell lung cancer, tumour boards, educational efforts, peer pressure[17]. Apparently, the initiative was regarded as a failure and was started again later on, in particular by the Commission on cancer of American Colleges of Surgeon (<http://www.facs.org/cancer/coc/categories.html>). This one defined several types of programs (Network Cancer Program, Community Hospital Comprehensive Program Cancer, Community Hospital Cancer Program...). The organisational aspects, the structure and the procedures of each one of these programs are included in standards. These standards correspond to the setting on paper of procedures to be followed by the whole oncology programme and are the subject of accreditation/certification. Beside the CHOP, the NCI also developed another type of programme: the CCOP more directed towards the participation of the oncology centers in the clinical trials but with also a goal of good practices diffusion (translational research program [18] and of improvement of quality (... program designed to ensures that state-of-the art cancer treatment and control technology is available to community physicians). These initiatives obtained overall positive results [19]. The handbooks used for the CCOP are clinical protocols of research which do not correspond to the multidisciplinary definition of oncology handbook

Network, coordination: A project developed by the French in 2003[20], deserves a particular attention, because it unifies in only one approach, the development of guidelines (by the ANAES), the use of standards (SOR of the FNCLCC), an approach based on a planning of the care (the plan of care), in a multidisciplinary context of network connecting the various levels of hospital care as well as the first line. All in all, this approach is very similar to the one described in the Belgian Royal Decree on the healthcare programme in oncology.

Oncology plans: Several countries, areas, provinces, [21]... develop quality plans. The majority of this plans are concerned with public health matters and do not correspond to the concept of handbook quality. However, in certain cases, as in Andalusia Spain, the plan is more detailed by type of cancer, is making reference to the existing guidelines or protocols, is mentioning organisational aspects and standards [22].

Based on this literature review concerning the quality handbooks in oncology, a structure for the national oncology handbook is proposed, in collaboration with the Working party of the College of physicians for oncology.

2.4 STRUCTURE OF THE MULTI-DISCIPLINARY HANDBOOK IN ONCOLOGY

2.4.1 Introduction

This is a national model of multidisciplinary handbook in oncology, developed by the College of oncology and the KCE. This model provides a framework allowing the oncology care programmes to specify their institutional features.

The **College of Oncology** is an official Belgian multidisciplinary council representing the medical specialties involved in cancer care. The College has been established by the law on the Oncology Healthcare Programmes and its members are appointed by ministerial decree. It is the task of the College to supervise the quality of care of adult cancer patients in Belgium through multidisciplinary consensus and to support the Cancer Care programs in their implementation of optimal cancer care.

Each Oncology Healthcare Programme possesses an **Oncology Handbook** in which the various aspects of cancer care are described. To facilitate the production of local Handbooks, the college has decided to create a National Template. This template will become progressively available online. The local Programs can use this template as the basis for their Handbook by complementing this with their local data and preferences.

The consultation of the Handbook, including the guideline sections will be free and open, both for professionals and the public, including patients.

Major sections of the Handbook are the guidelines on cancer care.

The guidelines are disease-oriented. In addition transversal guidelines are provided on subjects important for cancer care in general. In the making of these guidelines two essential elements have been observed: the level of international evidence and, where evidence is lacking, complemented by consensus among Belgian experts.

The Handbook is created by a Working party in collaboration with the KCE and the Belgian Public Health ministry. The working party is constituted of members of the college and co-opted members.

Cautionary notes

The Handbook and the guidelines are the product of extensive consultation. Nevertheless it may be possible that on certain aspects well founded dissention can exist. The guidelines are not a dictate but rather a beacon around which the cancer care givers and policymakers can orient their proper actions.

Also the proposed guidelines are not comprehensive and local programmes are required to complement these guidelines with their own preferences, which should also be supplemented by supportive evidence. Where evidence is lacking local expert preferences can be included. The guidelines also do not restrict options based on reimbursement criteria, especially if these are at odds with optimal care. Rather, the guidelines could be a reference for insurers to help orient there own policy. The College also declines any responsibility in the care of individual patients. The guidelines and the authors of these guidelines are not a substitute for individual professional competence in the diagnosis and treatment of cancer.

The College of Oncology advocates that cancer care should be administered by dedicated specialists, for the diagnostic, therapeutic and supportive aspects.

Following topics should be explicated in the multidisciplinary handbook in oncology:

- Listing of the infrastructure - services – staff
- Development process of the multidisciplinary handbook in oncology
- General strategy of the Oncology Care Programme
- General clinical approach
- Specific clinical approach by type of cancer
- Transversal themes
- Specific approach by speciality
- Organisational approach
- Description of procedure and frequency of updating the multidisciplinary handbook in oncology

Each of the topics is worked out in this model.

2.4.2 Listing of the infrastructure - services - staff

Listing of the services available in the Oncology Care Programme inside and outside the institution, and listing of the involved staff including name and function, according to the Royal Decree on Oncology Care Programme of march 21 2003 [1]:

Available infrastructure

- department of radiotherapy
- hospitalisation unit (headed by internist - oncologists)
- specific day hospital for cancer patients (headed by an internist - oncologist)
- site of the oncology pharmacy (which exceptionally can be located outside the principal pharmacy and next to treatment unit)

Available personnel, with official legal speciality

- name of oncology coordinator
- composition of the multidisciplinary commission of oncology and the executive board of the Oncology programme
- composition of the different working parties establishing the local guidelines for different cancer systems
- identification of all physicians involved in cancer care and specifically:
 - internist - oncologist (full time at each site)
 - radiotherapist (can be part time at participating site)
 - surgeon
 - haematologist
 - at least three of the following specialities: gastroenterology, pneumology, gynaecology, urology,
 - pathologist,
 - specialist in clinical biology,
 - radiologist and specialist in nuclear medicine,

- physician competent for oncology emergencies (internist and/or radiotherapist)
- identification of the head nurses specific for oncology and radiotherapy
- identification of the specialist in pain treatment
- specification of the palliative team and network
- composition of the pharmaceutical committees specific for oncology products name of the responsible pharmacist
- identification of the members of the psychosocial team
- identification of physical therapist, speech therapist and dietician

List of formal collaboration with other institutions (i.e. other oncology care programme)

- name of institution(s)
- name of the coordinator in these institutions and contact address

2.4.3 Development process of the handbook

The Oncology Care Programme has to include in its multidisciplinary handbook in oncology a report stating the following: writers of the multidisciplinary handbook in oncology, their affiliation, their function, number of meetings, history of development of the handbook including the update dates of the various components.

2.4.4 General strategy of the Oncology Care Programme

Following items should be stated: mission, vision, values, goals within 5 years, quality policy.

Example: Nice guideline for breast cancer:

(http://www.nice.org.uk/pdf/Improving_outcomes_breastcancer_manual.pdf)

Multidisciplinary team working:

All patients with breast cancer should be managed by multidisciplinary teams and all multidisciplinary teams should be actively involved in network-wide audit of processes and outcomes.

Multidisciplinary teams should consider how they might improve the effectiveness of the way they work. Some units should consider working together to increase the number of patients managed by the team.

Minimising delay:

No patient should have to wait more than four weeks for any form of treatment or supportive intervention.

Follow-up:

The primary aims of clinical follow-up should be to identify and treat local recurrence and adverse effects of therapy, not to detect metastatic disease in asymptomatic women. Long-term routine hospital-based follow-up should cease, except in the context of clinical trials.

Review of services for screened and symptomatic patients:

Each cancer network should review its arrangements for breast screening, with the goal of bringing services for screened and symptomatic patients into closer alignment. Networks should aim to achieve consistency in clinical policies, organisation and care, irrespective of the patient's point of entry into the system.

2.4.5 General clinical approach

The patient's medical file must include:

- personal and family history
- anamnesis
- complete physical examination
- staging (TNM with edition or other classification if specified in tumour specific guideline)
- plan of treatment following guidelines. If guidelines are not followed, a multidisciplinary oncology consultation must be foreseen.
- multidisciplinary oncology consultation: date and conclusion
- communication policy: the treating specialist in charge of the patient should communicate the treatment plan to the patient, his/her family and designated GP or other specialist. It is important to involve the patient in order to stimulate patient's autonomy.

2.4.6 Specific clinical approach by type of cancer

General guidelines for the following cancers are provided and detailed by organ except if the tumour is not treated in the setting (with the date of last update):

- cancer of head and neck
- cancer of the digestive tract
- cancer of the respiratory tract and mesothelioma
- breast cancer
- gynaecologic cancer
- genitourinary cancer
- skin cancer (melanoma, non melanoma)
- brain tumours
- sarcomas
- thyroid cancer
- neuroendocrine cancer
- haematological malignancies

These guidelines are to be used for diagnosis, staging, treatment, supportive care, follow - up, recurrences treatment and care, palliative treatment of patients to be .

The guidelines must conform to the national recommendations of the College of Oncology when provided. These national recommendations are evidence - based in respect with the scientific literature (critical appraisal on the basis of AGREE e;g). The national recommendations have been developed by the College of Oncology and the KCE in cooperation with experts of the involved national scientific and professional societies. They contain the state of the art for diagnostic and treatment strategies of the various cancers but without technical details on specific methods. Therefore, the guidelines contain references and hyperlinks to other guidelines or websites providing complementary or supplemental information. This will be the case for more detailed information on imaging and pathological examination as well as technical aspects for which guidelines have been developed by other Colleges or scientific institutions. The guidelines are accessible on the web page of the College for Oncology.

The national recommendations provide a minimal and evidence – based framework wherefrom local tailored guidelines can be developed. The local guidelines can and often should contain more detailed specifications, according to local insights in existing published evidence or according to local prospective clinical trials.

Therefore these local guidelines complement the national recommendations. However, any statement in the local guidelines in contradiction with the national recommendations should be supported by cited evidence.

A care plan for tumours that are treated in other institutions must be detailed. For example in the absence of radiotherapy on site or when specialized care is needed.

2.4.7 Transversal themes

Names and function of the responsible for the following domains:

- patient information procedures
- psychological approach of the patient and his/her family
- pain management
- nutritional approach
- specific pharmaceutical procedures
- clinical trials participation procedures (name of data-nurse, name of president of the ethical commission)
- rehabilitation
- bedsores prevention
- specific cultural approach
- palliative care and end of life approach

Point out which guidelines and/or standards are used for each topic, if any.

2.4.8 Specific approach by speciality

When possible recommendations elaborated by the scientific groups or societies, Colleges or other Belgian working parties should be included and consulted. At the website of the College of Oncology, links are made to these recommendations when available. It is recommended to include following recommendations multidisciplinary handbook in oncology:

- histopathology: procedures of staging, reporting...
- radiology and nuclear medicine
- surgery (if needed): policy of communication towards the patient and his/her family, preoperative assessment, health education (stomas...)...
- radiotherapy (if needed): policy of communication towards the patient and his family, calculation of the dose amount/distribution, toxicity, treatment of side-effects
- chemotherapy (if needed): policy of communication towards the patient and his family, toxicity, treatment of side-effects
- clinical biology
- pharmacy and medication
- other medical or paramedical specialities

Point out which guidelines and/or standards are used for each topic, if any.

2.4.9 Organisational approach

The following points must be specified in the multidisciplinary handbook in oncology:

- internal multidisciplinary coordination: multidisciplinary team: (see point I)
 - identification of coordinator(s)
 - frequency of meetings
 - communication with pathologist, radiologist, nuclear medicine, clinical biology, analyses and follow-up of the recorded indicators
- external coordination
 - policy of communication with the general practitioners
 - policy of communication with home care
 - policy of communication with other hospitals
 - policy of communication with palliative platforms and institutions with which formal agreements were made
- policy of patient participation in the decision-making process
- policy for quality of care: quality evaluation procedures, risk management, quality promotion
- data management:
 - indicators (with at least the percentage of observed and the number of divergences with guidelines recommendations)
 - links with external databases (Cancer registry)
 - control procedures used for data management
- policy of staff continuing medical education
 - description
 - frequency of case reviews...

2.4.10 Description of procedure and frequency of updating the multidisciplinary handbook in oncology

A brief description of the procedure for updating the multidisciplinary handbook in oncology is to be foreseen. The frequency of the updating should also be explicitly stated.

3 GUIDELINES DEVELOPMENT

3.1 INTRODUCTION

An important part of the quality handbook in oncology is to bring together the guidelines used by the oncology care programmes. In order to help the oncology programmes to rest on high quality guidelines, the working party of the college of physicians for oncology has decided to review the existing guidelines for all tumours sites in the scientific literature, to make a critical appraisal based on the EBM and to adapt them to the Belgian situation. The final objective is to propose to the oncology programme a set of guidelines with recommendations based on the existing evidence. These guidelines represent the minimal criteria to be followed by the oncology programmes, taking into account the specific situation of each patient and will represent the basis for the development of clinical pathways. Every oncology programme will then have to add its own recommendations based on a local consensus when high level evidence doesn't exist in the scientific literature.

In order to review the existing guidelines, the college of Physicians for Oncology has requested the help of the KCE. It has been decided to start with colorectal tumour guideline, because it is a frequent cancer in the population and with testicular tumour because it is a tumour with a high percentage of recovery, when correctly managed. The expected health benefits of this work is to improve the general quality of cancer management for the topics covered, by spreading among all oncology programs high quality guidelines in a first step, and then by developing quality indicators based on these guidelines, in a second step.

The target population of these guidelines is made by all the physicians working in an oncology care programme. Despite the fact that is has not been developed in first instance for these professionals, it could surely be of interest for the non medical staff of the oncology programme and for the GPs. The expected health benefits of this work is to improve the general quality of cancer management for the topics covered, by spreading among all oncology programs high quality guidelines in a first step, and then by developing clinical pathways and quality indicators based on these guidelines, in a second step.

The College of Oncology represents all the medical disciplines involved in the diagnosis and treatment of cancers. The working party "guidelines development" of the College is in charge of developing high quality guidelines. For each tumour, the working party has appointed an expert to develop the guideline, with the help of the KCE. It has been decided to submit the draft of all the guidelines developed to the concerned scientific societies. There is no direct and specific involvement of other healthcare professionals in the development of this work. Nevertheless, the point of view of these professionals has been taken into account through the review of the guidelines reviewed to build up these presented here.

3.2 REVIEW BY EXPERTS

As stated before, the guidelines were reviewed by a physician expert in the concerned tumour and appointed by the working party of the College of oncology, by the different scientific societies concerned by the guidelines topic, by the College of oncology as a whole, and finally, validated by 3 experts.

3.3 UPDATING AND DISSEMINATION

No formal procedure to update the guidelines has been decided. However, the working party “guidelines development” of the college of oncology bears the responsibility to start an updating procedure anytime major changes in the scientific evidence occurs.

The guidelines will be sent in a paper format to all oncology programmes. Moreover, in order to develop the dissemination, an electronic version available on the internet will be proposed.

3.4 FINAL REMARKS

- The cost effectiveness of these guidelines recommended procedures have not been studied. It will be one of the objectives of the development of a clinical pathway.
- The different management options are presented in the flow chart presented at the beginning of each guideline. More details are presented in the text when necessary.
- The following institutions have participated in the elaboration or the reviewing process of the guidelines:
 - College of Oncology:
 - Belgian Society of medical Oncology (BSMO)
 - Belgian Group of Digestive Oncology (BGDO)
 - Belgian Association of urology (BAU) Working Group Oncology
 - College of medical imaging

The name, affiliation and potential conflict of interest of the persons involved in the development of this work are presented in the first page of this report:

3.5 COLORECTAL CANCER GUIDELINE

3.5.1 Clinical questions

The clinical questions of this guideline are the following:

- What is the evidence for colon and rectal cancers diagnosis management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for colon and rectal cancers therapy management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for colon and rectal cancers follow up management?

3.5.2 Methodology

3.5.2.1 *Search for evidence*

First the existing guidelines were searched in October 2004 using as keywords “colon, rectum and colorectal with cancer and neoplasm” (MESH terms and text). The National Guideline Clearinghouse (114 references) and Pubmed (131 references, limit: practice guideline) were searched, without date limit or language restriction.

The websites of known agencies were systematically searched (Europe: ESMO, The Netherland: Oncoline, UK: NICE, The association of coloproctology of GB and Ireland, Scotland: SIGN, CANADA: Ontario Cancer care, USA: NCCN, NIC, ASCO, American Society of colon & rectal surgeons, France: ANAES, FNCLCC, Singapore: Ministry of Health). Two search engines were also searched (Google and Journalservice for medics) with the same keywords than mentioned earlier.

Finally a search for systematic reviews in the Cochrane database and in DARE (19 references) was performed. An update of the search was performed in December 2005 but did not yield new significant publication.

3.5.2.2 *Selection*

The guidelines on diagnosis, treatment and follow up of colorectal cancers were reviewed. In order to exclude all opinions papers or narrative reviews, the guidelines with no mention of a clear evidence-based system to grade the recommendations, were excluded. The guidelines were selected and appraised by two experts, using the AGREE instrument. All disagreements were resolved by consensus. The results of the appraisal are presented in appendix I. The guidelines with an overall assessment of “strongly recommended” or “recommended” were selected and used to develop a synthesis which was discussed and reviewed by the expert appointed by the working party of the College of Oncology, in order to adapt the recommendations to the Belgian situation. A special interest was brought to the methods used in all the reviewed guidelines to search and select the evidence (databases, search strategies, selection criteria, selection methods). The synthesis was build using the guidelines rated as “strongly recommended” as basis. For every point, the recommendations of the guidelines rated “recommended with provisos”, if any, were also cited. In case of disagreement between different guidelines, the recommendations of the guidelines rated “strongly recommended” were always preferred on the others. For specific points for which no recommendations were found in the “strongly recommended” guidelines, the evidence of “recommended guidelines” or coming from good systematic reviews have been used.

3.5.2.3 Grading of recommendations

Each guideline developer has his own evidence grading system. To synthesize the different systems, a correspondence table is presented hereunder. The key to evidence statements and grades of recommendations used in the selected guidelines are presented in the appendices.

KCE grade	SIGN	NICE	ASCO	NCI	NCCN	SMOH
A	A	A	A	I		A
B	B & C	B	B	2 & 3i & 3ii		B
C	D	C	C & D	3iii	I & 2A	C

A = Evidence derived from RCT or meta-analysis or systematic review of RCT.

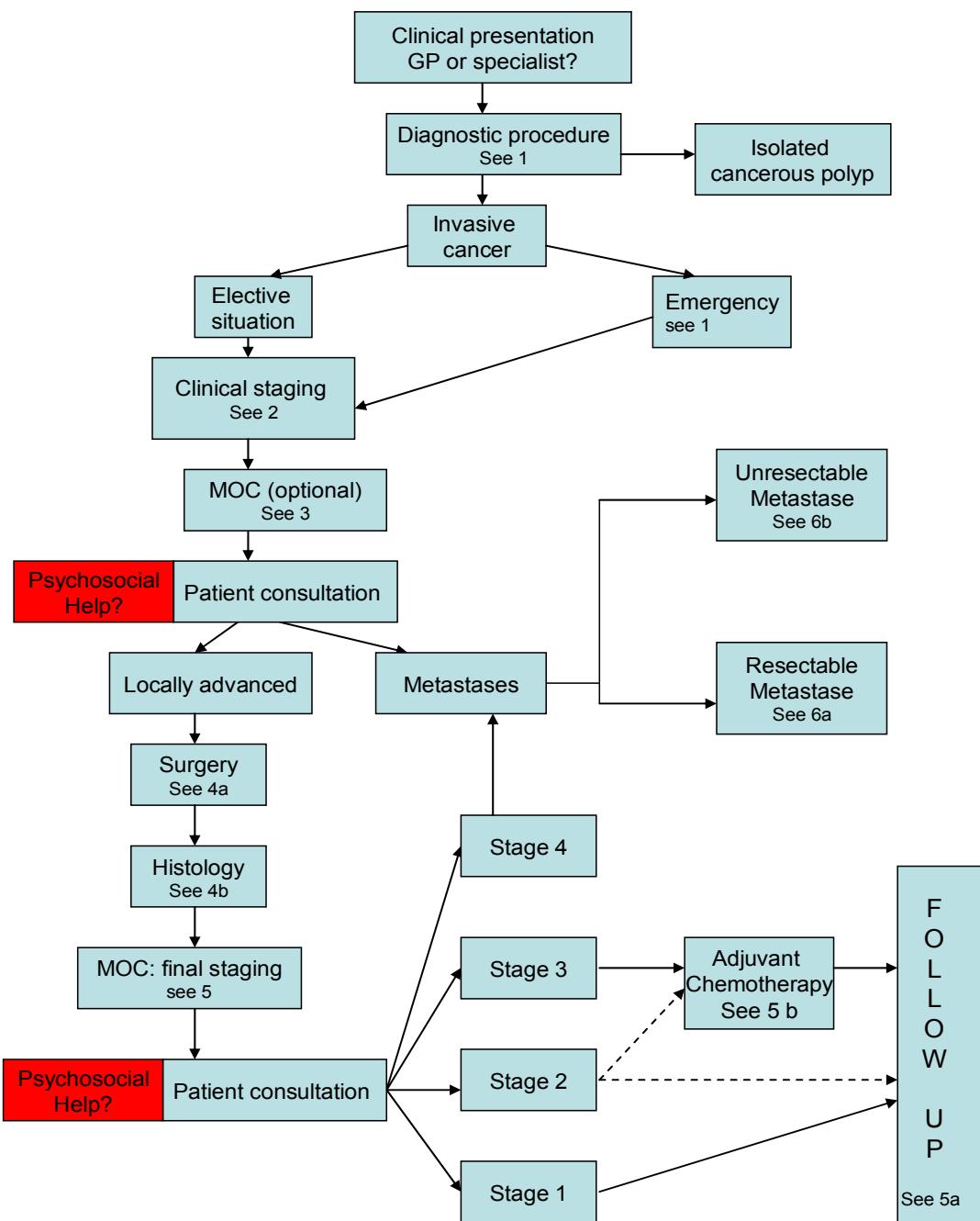
B = Evidence from non-randomised controlled trials or observational studies.

C = Professional consensus, or case reports, case series.

For presentation reasons, grade A recommendations, with a very high level of evidence, are put in bold letter; grade B recommendations with a high level of evidence are put in normal letters and grade C recommendations, principally based on consensus are put in italic letters. Due to their weak level of evidence, these last recommendations could be changed in a near future depending on the body of evidence. Nevertheless they are presented in this work because they are based on a large consensus within the scientific community.

3.5.3 Colon cancer guideline

3.5.3.1 GENERAL ALGORITHM



3.5.3.2 Introduction

The guideline presented covers diagnosis, treatment and follow up of colon cancer. It is based on the existing international guidelines which have been critically appraised (see Appendix 1) and on the consensus of national societies.

We will go through the following topics:

- Diagnosis
- Clinical Staging
- Multidisciplinary team meeting (optional)
- Treatment of non-metastatic disease
 - surgery
 - pathology
- Final staging - Multidisciplinary team meeting
 - follow up
 - adjuvant therapy
- Treatment of metastatic disease
 - resectable metastases
 - unresectable metastases

The grade of recommendation is stated in the text as follow:

GR A = Evidence derived from RCT or meta-analysis or systematic review of RCT

GR B = Evidence from non-randomised controlled trials or observational studies

GR C = *Professional consensus, or case reports or case series*

I. Diagnosis

Patient's history

A personal history has to be taken.

The diagnostic procedure is generally indicated for patients with the following symptoms [23-25](**GR B**):

- **For all ages:** rectal bleeding with change in bowel habits to looseness or increased frequency over a period of six weeks and/or palpable abdominal mass and/or iron-deficiency anaemia without overt cause.
- **Over 60 years:** rectal bleeding without any symptoms, or change in bowel habits to looseness or increased frequency.

A family history has to be taken:

In order to determine the high risk groups, a family history of at least two generations should be taken to every patient with colon cancer [23, 24] (**GR B**).

If there are 1 or 2 family members diagnosed with colon cancer, if the patient is less than 50 years old or if the patient has concomitant or previous ovarian or endometrium cancer, a 3 generations extensive family history is required (**GR C**).

Patients with suspected hereditary conditions should be oriented towards a Genetic Service [23] or a Familial Cancer Clinic (**GR C**).

Examination

- x a complete clinical examination (**GR C**).
- x Colonoscopy with biopsy is recommended for every patient with suspected colon cancer [23, 24] (**GR C**). If not possible, an enema[26] has to be performed [23, 24] (**GR B**).
 - x Importance of good orientation of the specimen (quality criteria for endoscopist and pathologist). The biopsy must give answers to the following questions [23, 24] (**GR B**):
 - malignant or benign?
 - is it a carcinoma within a polyp or an invasive cancer?
 - what is the differentiation grade of the tumour?

DIAGNOSTIC CONCLUSION

At the end of the diagnostic procedure, an answer must be given to the following questions:

- Is it an isolated cancerous polyp which has been completely resected? If the answer is yes (Tis stage), there is no other treatment except if there is histological evidence of tumour at, or within 1 mm of, the resection margin, there is lymphovascular invasion or the invasive tumour is poorly differentiated [23, 27, 28] (**GR B**). (All polyps have to be sent to the pathologist for analysis(**GR C**)).
- Is it a recurrence of a previous colon cancer [28] (**GR C**)?
- Is it an invasive cancer(**GR C**)?

EMERGENCY

In case of emergency (bleeding, perforation, obstruction...) routine procedures may be neglected and immediate resection should be considered in optimal candidates [23, 24, 29, 30] (**GR B**).

In that case, intraoperative liver ultrasound and postoperative imaging is necessary [23] (**GR B**).

2. Clinical staging

Following staging examinations are recommended:

- CEA level [28, 31] (**GR C**).
- In general, thoraco-abdominal Contrast CT is recommended [24, 31] (**GR C**).
 - Liver [23, 24]: MRI is an alternative. US can be considered when Contrast CT or MRI are not possible(**GR B**).
 - Chest [23, 24]: CT scan [32] (**GR B**)
 - Lymph nodes: CT scan [24, 31] (**GR B**)

cTNM: pre-treatment clinical classification, based on clinical examination, imaging, endoscopy, biopsy, surgical exploration or other.

3. First Multidisciplinary Team Meeting (MOC) – optional

- The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging [24] (**GR C**).
- If possible, the general practitioner (GP) of the patient should attend this meeting [24]. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient(**GR C**).
- Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision [23, 24] (**GR C**). Information about local support services should be made available to both the patient and their relatives[23, 24] (**GR C**). Healthcare professionals should respect patients' wishes to be involved in their own management [23, 24] (**GR B**).
- The need for psychosocial help must be evaluated and offered if required [24] (**GR B**).

4. Treatment of non-metastatic disease

a. Surgery :

If no metastases are found, the patient is oriented to surgery which remains the only curative option [23, 24, 27, 28, 33] (**GR C**).

- x preoperative preparation:

A preoperative risk assessment should be performed according to the appropriate guidelines (see [http://www.kenniscentrum.fgov.be
/fr/Publications.html](http://www.kenniscentrum.fgov.be/fr/Publications.html)).

Before undergoing surgery, the patient should have venous thromboembolism prophylaxis with LMW Heparin(**GR B**) and antibiotic prophylaxis (single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia) [23, 24, 30, 31, 33] (**GR A**).

- x surgery:

There is little evidence relating to the radicality of colon cancer surgery [23]. Where a respectable organ (eg. kidney, ureter, duodenum, liver, stomach, bladder, uterus or vagina) is involved by the primary tumour, careful consideration should be given to removal (partial or total as appropriate) of that organ. Colon cancers adherent to adjacent structures should be resected en bloc [23, 31, 33] (**GR C**). Bilateral oophorectomy is advised when one or both ovaries are grossly abnormal or involved with contiguous extension of the colon cancer. However, prophylactic oophorectomy is not recommended [31] (**GR C**).

Lymph nodes at the origin of feeding vessel should be identified for pathologic examination (**GR C**).

Lymph nodes outside the field of resection considered suspicious should be biopsied or removed [28, 31, 33] (**GR C**).

Tumour tissue left behind indicate an incomplete (R2) resection. The surgery report must indicate if the resection was complete (R0 - R2) [24, 28] (**GR C**).

The extent of resection of the colon should correspond to the lymphovascular drainage of the site of the colon cancer [31, 33] (**GR C**).

Synchronous colon cancers can be treated by two separate resections or subtotal colectomy [31, 33] (**GR C**).

b. Histology procedure: (see pathologists guideline)

The exact procedure to examine a colon resection specimen is described in a consensus text made by the gastrointestinal pathologists[34].

The pathologist should search for lymph nodes in the resection specimen and the number found should be noted [24] (**GR B**). In patients with colon cancer who are treated with curative intent, 12 or more nodes should normally be examined; if the median number is consistently below 12, the surgeon and the pathologist should discuss their techniques [24] (**GR B**). Patients with inadequately sampled nodes could be offered adjuvant chemotherapy [35] (**GRC**).

All reporting of colon cancer specimens should contain gross description, histology type, differentiation by predominant area, margins (tumour involvement), metastatic spread, background abnormalities, staging [23, 24] (**GR B**).

5. Final Staging

Colon cancer should be staged following the TNM staging system [27, 28, 31] (**GR B**) :
pTNM: post-surgical histopathological classification.

T - Primary tumour

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the subserosa, or into nonperitonealized pericolorectal or perirectal tissues
T4	Tumour directly invades other organs or structures or perforates visceral peritoneum

N – Nodal status

Nx	Regional lymph nodes cannot be assessed.
N0	No metastases in regional lymph nodes.
N1	Metastases in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

A tumour nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

M – Distant metastases

Mx	Presence or absence of distant metastases cannot be determined
M0	No distant metastases detected
M1	Distant metastases detected

G – Histologic grade

Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4	N0	M0
Stage III A	T1 or T2	N1	M0
Stage III B	T3 or T4	N1	M0
Stage III C	Any T	N2	M0
Stage IV	Any T	Any N	M1

The final staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports available for a given patient [24, 28] (**GR C**).

If possible, the general practitioner of the patient should attend this meeting. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient[24] (**GR C**).

Depending on tumour stage, the further treatment options are decided [23, 24, 27, 28, 35-38] (**GR A**):

Stage I	Follow up (GR A)
Stage II	Chemotherapy is discussed based on risk assessment (ev. Adjuv online) (GR A)
Stage III	Absolute indication for chemotherapy (if no major objection) (GR A)
Stage IV	See point 6 (metastatic disease)

A written report with staging and treatment options is mandatory for each patient [30] (**GR C**).

a. Follow up procedure

Patients who have undergone curative resection for colorectal cancer should undergo formal follow up in order to facilitate the early detection of recurrence and/or metastatic disease [23, 24, 27, 28, 39-42] (**GR A**)

Although no absolute scientific prove of outcome benefit of an intensive follow up policy [19], we could recommend following strategy:

- Physician visit: every 3 to 6 months for the first 3 years after initial treatment, every 6 months during years 4 and 5 and then yearly for 5 years[32] (**GR C**);

- CEA every 3 months during 3 years if patient is candidate for surgery or systemic therapy[32] (**GR C**);
- CT thorax and abdomen at 3 months and every year during 3 years in patients at higher risk of recurrence[32, 43] (**GR C**).
- Colonoscopy after 3 years and every 5 years in average risk patients [32] (**GR C**).

PET should be performed in patients with a high clinical suspicion of recurrent disease associated with negative or equivocal (without clear positive conclusion) work up (high pre test probability):

- Suspicion of local recurrence of a colon cancer with equivocal CT, MRI and endoscopy.
- Exclusion or confirmation of metastasis in equivocal CT, MRI lesions (eg. indeterminate lymph nodes in the retroperitoneal space; a pulmonary or hepatic nodule).
- A rising CEA level.

see KCE HTA report on PET scan

<http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf> :

For detection and localization of local, hepatic and extra-hepatic recurrence, the diagnostic efficacy includes changes in patient management and therapeutic decision. In addition, there is limited evidence for cost-effectiveness. PET is indicated for localization of metastasis in case of increasing CEA level following surgery in a patient with colorectal cancer

b. Adjuvant therapy

As indicated in the final staging section, stage III colon cancer is an absolute indication for adjuvant chemotherapy(**GR A**). Different options, ie. infusional 5-fluorouracil in association with folinate, oral fluoropyrimidines, infusional 5-fluorouracil in association with folinate and oxaliplatin, [23, 24, 44, 45] (**GR A**) are available and reimbursed in Belgium (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm http://www.bcfi.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm).

The choice of a regimen for a given patient is based on his/her risk profile and the toxicity of the drugs (**GR C**). Various regimens are presented in the appendices.

6. Treatment of metastatic disease

a. Treatment of resectable metastases

Following therapeutic strategies can be proposed on the basis of the individual situation of the patient and his tumour [23, 24, 27, 28, 31] (**GR C**):

x surgery of the primary tumour and the metastasis in the same procedure,

x surgery of the primary tumour followed by:

- surgery of the metastasis, or
- chemotherapy and then surgery of the metastasis

CRITERIA FOR RESECTABILITY OF METASTASES[28]

Liver

Complete resection must be based on the anatomic location and the extent of disease, maintenance of hepatic function is required[28] (**GR C**)

There should be no unresectable extrahepatic sites of disease [28] (**GR C**).

The primary tumour must be controlled [28] (**GR C**).

Re-resection can be considered in selected patients [28] (**GR C**).

Resection is the treatment of choice for resectable liver metastases. Other techniques such as radiofrequency might be optional or complementary [28] (**GR C**).

Note: MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis[46] (**GR B**).

Lung

Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required[28] (**GR C**).

Resectable extra-pulmonary metastases do not preclude resection [28] (**GR C**).

The primary tumour must be controlled [28] (**GR C**).

Re-resection can be considered in selected patients [28] (**GR C**).

After resection, adjuvant chemotherapy can be considered [23, 24, 27, 28, 47-50] The decision is made on individual basis depending on the risk profile and health status. (**GR C**).

The patient assessment and decision about treatment options should preferably be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed[23, 24] (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started[23, 24] (**GR B**).

The follow up procedure is the same as for patients without metastasis.

b. Treatment of unresectable metastases

If the patient presents with symptoms related to the primary tumour (bleeding, obstruction...): resection of primary tumour followed by chemotherapy [23, 24, 31, 33] (**GR B**).

If the patient has no symptoms related to the primary tumour: chemotherapy [51] (**GR A**).

Each patient should receive an evaluation for first and second line chemotherapy [23, 27, 28, 50] (**GR A**). Today, therapy with oral fluoropyrimidines in monotherapy or infusional 5-fluorouracil in combination with either Irinotecan or Oxaliplatin is considered as standard (**GR C**). The decision on which regimen for a given patient is especially based on the performance status [23, 24, 28] (**GR A**).

Reevaluation of patients under treatment for metastatic disease should include an every 2 to 3 month CT assessment, always performed with the same tools for comparison reasons (**GR C**). MRI can be considered in specific conditions (**GR C**). At every evaluation the different treatment options must be discussed (**GR C**).

The patient assessment and decision about treatment options should preferably be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed[23, 24] (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started[24] (**GR B**).

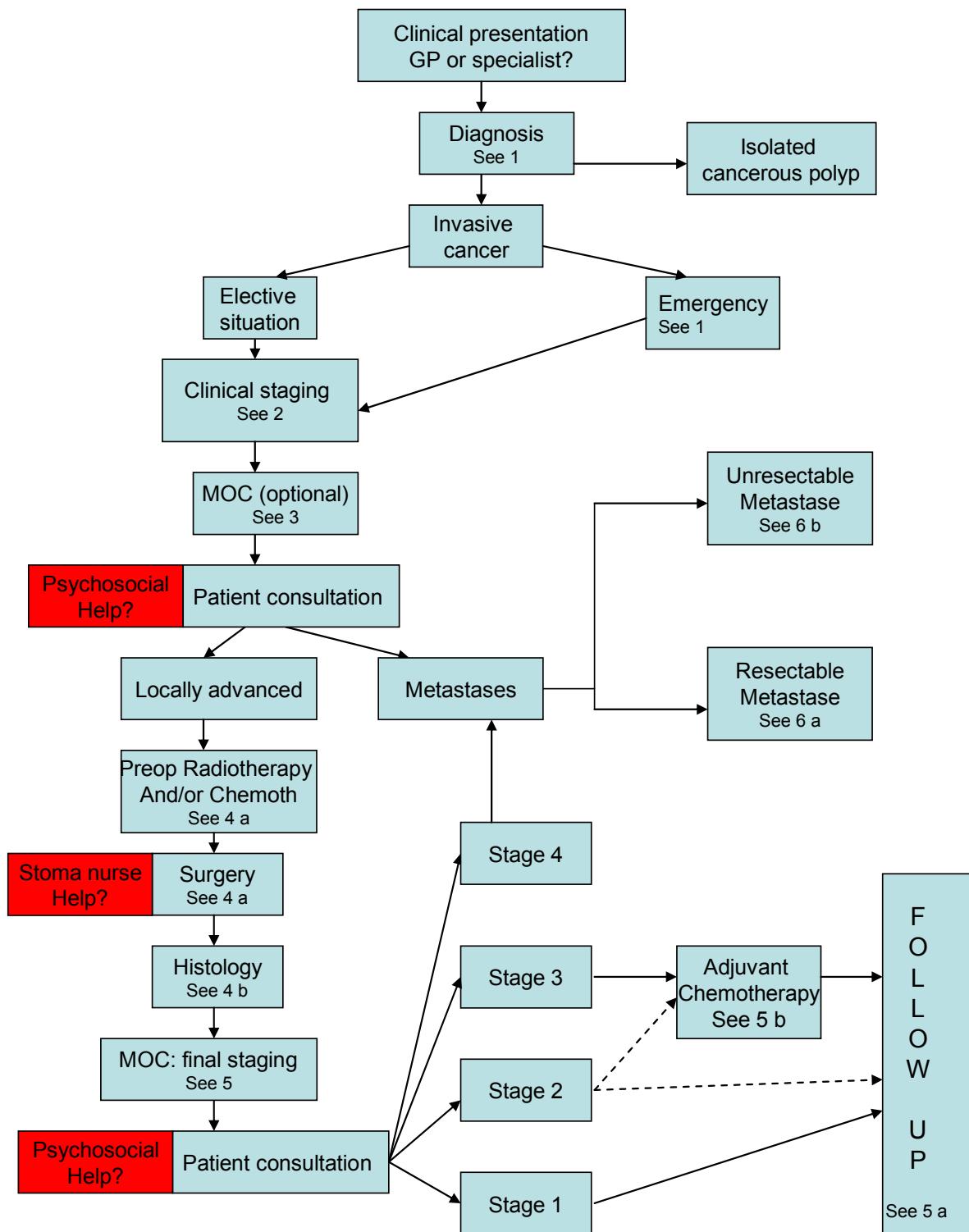
Patients with advanced colorectal cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management[23, 24] (GR C).

Palliative care specialists should be members of, and integrated with, colorectal cancer multi-disciplinary teams; their role includes the provision of education and advice for other health professionals and direct patient management[24] (GR C).

A patient in good health status and progressive under standard therapy should be proposed a clinical trial protocol [24] (GR C).

3.5.4 Rectum cancer guideline

3.5.4.1 GENERAL ALGORITHM



Introduction

The guidelines presented covers diagnosis, treatment and follow up of rectum cancer. It is based on the existing international guidelines which have been critically appraised (see Annex 1) and on the consensus of national societies. It's also important to mention the national, multidisciplinary project on rectal cancer PROCARE, www.procare.be

The definition of rectal tumours in this guideline is: tumours whose distal edge is seen within 16 cm from the anal verge as measured with a rigid recto-sigmoidoscope (Procare guideline)

We will go through the following topics:

- Diagnosis
- Clinical Staging
- Multidisciplinary team meeting (optional)
- Treatment of non-metastatic disease
 - a. surgery
 - b. pathology
- Final staging - Multidisciplinary team meeting
 - a. follow up
 - b. adjuvant therapy
- treatment of metastatic disease
 - a. resectable metastases
 - b. unresectable metastases

The grade of recommendation is stated in the text as follow:

GR A = Evidence derived from RCT or meta-analysis or systematic review of RCT

GR B = Evidence from non-randomised controlled trials or observational studies

GR C = Professional consensus, or case reports or case series

I. Diagnosis

Patient's history

A personal history has to be taken.

The diagnostic procedure is generally indicated for patients with the following symptoms [23-25] (**GR B**):

- For all ages: rectal bleeding with change in bowel habits to looseness or increased frequency over a period of six weeks and/or palpable abdominal mass and/or iron-deficiency anaemia without overt cause.
- Over 60 years: rectal bleeding without any symptoms, or change in bowel habits to looseness or increased frequency.

A family history has to be taken.

In order to determine the high risk groups, a family history of at least two generations should be taken to every patient with colon cancer[23, 24] (**GR B**).

If there are 1 or 2 family members diagnosed with colon cancer, if the patient is less than 50 years old or if the patient has concomitant or previous ovarian or endometrium cancer, a 3 generations extensive family history is required (**GR C**).

Patients with suspected hereditary conditions should be oriented towards a Genetic Service[23] or a Familial Cancer Clinic (**GR C**).

Examination

- x A complete clinical examination (**GR C**).
- x Colonoscopy with biopsy is recommended for every patient with suspected rectal cancer[23, 24] (**GR C**). If not possible, an enema [26] has to be performed[23, 24] (**GR B**).
- x Importance of good orientation of the specimen (quality criteria for endoscopist and pathologist). The biopsy must give answers to the following questions[23, 24] (**GR B**):
 - malignant or benign?
 - is it a carcinoma within a polyp or an invasive cancer?
 - what is the differentiation grade of the tumour?

DIAGNOSTIC CONCLUSION

At the end of the diagnostic procedure, an answer must be given to the following questions:

- Is it an isolated cancerous polyp which has been totally resected? If the answer is yes (Tis stage), there is no other treatment except if there is histological evidence of tumour at, or within 1 mm of, the resection margin, there is lymphovascular invasion or the invasive tumour is poorly differentiated[23, 27, 28] (**GR B**). (All polyps have to be sent to the pathologist for analysis (**GR C**)).
- Is it a recurrence of a previous rectal cancer [28] (**GR C**)?
- Is it an invasive cancer (**GR C**) ?

EMERGENCY

In case of emergency (bleeding, perforation, obstruction...) routine procedures may be neglected and immediate resection should be considered in optimal candidates[23, 24, 29, 30] (**GR B**).

In that case, intraoperative liver ultrasound and postoperative imaging is necessary[23] (**GR B**).

2. Clinical staging

Following staging examinations are recommended:

To detect metastases, the following examinations are recommended:

- CEA level[28, 31] (**GR C**).
- For staging, the primary choice is thoraco-abdominal Contrast CT [24, 31] (**GR C**).
- Liver[23, 24]: MRI is an alternative. US can be considered when Contrast CT or MRI are not possible(**GR B**).
- Chest[23, 24]: CT scan [32] (**GR B**).
- Adenopathy: CT scan [24, 31] (**GR B**).

cTNM: pre-treatment clinical classification, based on clinical examination, imaging, endoscopy, biopsy, surgical exploration or other.

3. First Multidisciplinary Team Meeting (MOC) - optional

- The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging[24] (GR C).
- If possible, the general practitioner of the patient should attend this meeting[24]. If not, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient(GR C).
 - Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision[23, 24] (GR C). Information about local support services should be made available to both the patient and their relatives[23, 24] (GR C).Healthcare professionals should respect patients' wishes to be involved when making plans about their own management[23, 24] (GR B).
- The need for psychosocial help must be evaluated and offered if required[24] (GR B).

4. Treatment of non-metastatic disease

a. Surgery

If no metastases are found, the patient is oriented to surgery which remains the only curative option[23, 24, 28, 33, 52] (GR C).

x preoperative radio/chemotherapy:

- Preoperative radiotherapy, planned with 3 or 4 fields (and not parallel opposed fields), should be considered in patients with operable rectal cancer[23, 24, 53-55] (. *Chemotherapy could be given synchronously with radiotherapy[23, 24, 28, 52, 55]* (GR C). *The regimens usually used are bolus FUFA or continuous fluorouracil (Procare guideline)* (GR C). *The patient with T1-2 rectal cancer cStage I in whom an adequate TME procedure is performed does not need neoadjuvant therapy. Neoadjuvant therapy is recommended in all other cases, except for tumours located at less than 6 cm from the anal verge or with a Circumferential Resection Margin less than 5 mm (Procare guideline)* (GR C).
- Postoperative radiotherapy should be considered in patients with rectal cancer who did not receive preoperative radiotherapy (e.g. case of emergency) and who are at high risk of local recurrence[23, 54, 55] (GR C).
 - YTNM: classification after induction therapy;

x preoperative preparation:

- A preoperative risk assessment should be performed according to the appropriate guidelines (see <http://www.kenniscentrum.fgov.be/fr/Publications.html>).
- Before undergoing surgery, the patient should have venous thromboembolism prophylaxis with LMW Heparin (GR B) and antibiotic prophylaxis (single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia)[23, 24, 30, 31, 33] (GR A).

x surgery: (see Procare guideline)

- The safe margin between the lower end of the tumour and the rectal stump must be greater than or equal to 2 cms [55] (**GR B**). An appropriate mesorectal excision, depending on the localization of the tumour, has an impact on the rate of local recurrences[23, 28, 52] (**GR B**).
- There is currently no indication for extensive pelvic nodal clearance[55].Lymph nodes at the origin of feeding vessel should be identified for pathologic examination.Lymph nodes outside the field of resection considered suspicious should be biopsied or removed[28, 31, 33] (**GR C**).
- Tumour tissue left behind indicates an incomplete (R2) resection. The surgery report must indicate if the resection was complete (R0 R2)[24, 28] (**GR C**).

b. Histological procedure: (see pathologists guideline)

The exact procedure to examine a colon resection specimen is described in a consensus text made by the gastrointestinal pathologists[34].

The pathologist should search for as many lymph nodes as possible in the excised specimen and the number found should be noted[24] (**GR B**). In patients with rectum cancer who are treated with curative intent, 6 or 8 nodes should normally be examined; if the median number is consistently below 8, the surgeon and the pathologist should discuss their techniques[24] (**GR B**). Patients with inadequately sampled nodes could be offered adjuvant chemotherapy[35] (**GR C**).

All reporting of rectal cancer specimens should contain gross description, histology type, differentiation by predominant area, margins (tumour involvement), metastatic spread, background abnormalities, staging[23, 24] (**GR B**).

5. Final Staging:

Rectum cancers should be staged using the TNM staging system[28, 31, 52] (**GR B**):

pTNM: post-surgical histopathological classification

T - Primary tumour

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the subserosa, or into nonperitonealized pericoloc or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N – Nodal status

Nx	Regional lymph nodes cannot be assessed.
N0	No metastases in regional lymph nodes.
N1	Metastases in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

A tumour nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

M – Distant metastases

Mx	Presence or absence of distant metastases cannot be determined
M0	No distant metastases detected
M1	Distant metastases detected

G – Histologic grade

Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4	N0	M0
Stage III A	T1 or T2	N1	M0
Stage III B	T3 or T4	N1	M0
Stage III C	Any T	N2	M0
Stage IV	Any T	Any N	M1

The final staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports available for a given patient [24] (**GR C**).

If possible, the general practitioner of the patient should attend this meeting. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient[24] (**GR C**).

Depending on the tumour stage, the further treatment options are decided[23, 24, 28, 35, 52] (**GR A**):

Stage I	Follow up (GR A)
stage II	Chemotherapy is discussed based on risk assessment (ev. Adjuv online) (GR A)
stage III	Absolute indication for chemotherapy (if no major objection) (GR A)
stage IV	See point 6 (metastatic disease)

A written report with staging and treatment options is mandatory for each patient[30] (**GR C**).

a. Follow up procedure

Patients who have undergone curative resection for colorectal cancer should undergo formal follow up in order to facilitate the early detection of recurrence and/or metastatic disease [23, 24, 27, 28, 39-42] (**GR A**)

Although no absolute scientific prove of outcome benefit of an intensive follow up policy [19], we could recommend following strategy:

- Physician visit: every 3 to 6 months for the first 3 years after initial treatment, every 6 months during years 4 and 5 and then yearly for 5 years[32] (**GR C**);
- CEA every 3 months during 3 years if patient is candidate for surgery or systemic therapy[32] (**GR C**);
- CT thorax and abdomen at 3 months and every year during 3 years in patients at higher risk of recurrence[32, 43] (**GR C**).
- Colonoscopy after 3 years and every 5 years in average risk patients [32] (**GR C**).

PET should be performed in patients with a high clinical suspicion of recurrent disease associated with negative or equivocal (without clear positive conclusion) work up (high pre test probability):

- Suspicion of local recurrence of a colon cancer with equivocal CT, MRI and endoscopy.
- Exclusion or confirmation of metastasis in equivocal CT, MRI lesions (eg. indeterminate lymph nodes in the retroperitoneal space ; a pulmonary or hepatic nodule).
- A rising CEA level.

(see KCE HTA report on PET scan:
<http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf>

For detection and localization of local, hepatic and extra-hepatic recurrence, the diagnostic efficacy includes changes in patient management and therapeutic decision. In addition, there is limited evidence for cost-effectiveness. PET is indicated for localization of metastasis in case of increasing CEA level following surgery in a patient with colorectal cancer.

b. Adjuvant therapy

As indicated in the final staging section, stage III rectal cancer is an absolute indication for adjuvant chemotherapy(**GR A**). Different options, ie. infusional 5-fluorouracil in association with folinate, oral fluoropyrimidines, infusional 5-fluorouracil in association with folinate and oxaliplatin, [23, 24, 44, 45] (**GR A**) are available and reimbursed in Belgium (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm http://www.bcfi.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm). Various regimens are presented in the appendices.

The choice of a regimen for a given patient is based on his/her risk profile and the toxicity of the drugs.

Adjuvant radiotherapy combined with chemotherapy could be an option, although there is no clear evidence that this combination improves survival[56] (**GR C**).

6. Treatment of metastatic disease

a. Treatment of resectable metastases:

Following therapeutic strategies can be proposed on the basis of the individual situation of the patient and his tumour[23, 24, 27, 28, 31] (**GR C**):

- × surgery of the primary tumour and the metastasis in the same procedure,
- × surgery of the primary tumour followed by:
 - surgery of the metastasis, or
 - chemotherapy and then surgery of metastasis

CRITERIA FOR RESECTABILITY OF METASTASES[28]

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of noble hepatic function is required[28] (**GR C**).
- There should be no unresectable extrahepatic sites of disease [28] (**GR C**).
- The primary tumour must be controlled[28] (**GR C**).
- Re-resection can be considered in selected patients[28]

Resection is the treatment of choice for resectable liver metastases. Other techniques such as radiofrequency might be optional or complementary [28] (**GR C**).

Note: MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis[46] (**GR B**).

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required[28] (**GR C**).
- Resectable extra-pulmonary metastases do not preclude resection[28] (**GR C**).
- The primary tumour must be controlled [28] (**GR C**).
- Re-resection can be considered in selected patients [28] (**GR C**).

After resection, adjuvant chemotherapy can be considered[23, 24, 27, 28, 47-50] The decision is made on individual basis depending on the risk profile and health status (**GR C**).

The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed[23, 24] (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started[23, 24] (**GR B**).

The follow up procedure is the same than that for patients without metastasis.

b. Treatment of unresectable metastases

If the patient presents with symptoms related to the primary tumour (bleeding, obstruction...): resection of primary tumour followed by chemotherapy[23, 24, 31, 33] (**GR B**).

If the patient has no symptoms related to the primary tumour: chemotherapy[51] (**GR A**). Each patient should receive an evaluation for first and second line chemotherapy [23, 27, 28, 50] (**GR C**). Today, therapy with oral fluoropyrimidines in monotherapy or infusional 5-fluorouracil in combination with either Irinotecan or Oxaliplatin is considered as standard (**GR C**). The decision on which regimen for a given patient is especially based on the performance status [23, 24, 28] (**GR A**).

Reevaluation of patients under treatment for metastatic disease should include an every 2 to 3 month CT assessment, always performed with the same tools for comparison reasons (**GR C**). MRI can be considered in specific conditions (**GR C**). At every evaluation the different treatment options must be discussed (**GR C**).

The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed[23, 24] (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started [24] (**GR B**).

Patients with advanced colorectal cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management[23, 24] (**GR C**).

Palliative care specialists should be members of, and integrated with, colorectal cancer multi-disciplinary teams; their role includes the provision of education and advice for other health professionals and direct patient management[24] (**GR C**).

A patient in good health status and progressive under standard therapy should be proposed a clinical trial protocol[24] (**GR C**).

3.5.5 Quality control

The good utilization of a guideline has to be evaluated. Therefore, a guideline has to be accompanied with quality control criteria.

These criteria should at least assess the following steps of the algorithm:

- clinical staging process
- surgery process
- histology process
- adjuvant chemotherapy and other treatments

For each step, quality indicators will be developed. In 2006, the KCE will start a project with the objective to develop and test quality indicators for rectal cancer. It will be the first tumour for which these kind of indicators will be tested and others will follow.

3.6 TESTICULAR CANCER GUIDELINE

3.6.1 Clinical questions

The clinical questions of this guideline are the following:

- What is the evidence for testicular cancer diagnosis management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for testicular cancer therapy management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for testicular cancer follow up management?

3.6.2 Methodology

3.6.2.1 *Search for evidence*

The keywords used for testicular cancer were “testicular with cancer and neoplasm”. The National guideline Clearinghouse (1 reference) and Pubmed (11 references, limit: practice guidelines) were searched in December 2004 without date limit or language restriction. The websites of known agencies were systematically searched (Europe: ESMO, European Association of Urology, The Netherlands: Oncoline, UK: NICE, Scotland: SIGN, CANADA: Ontario Cancer care, USA: NCCN, NIC, ASCO, France: ANAES, FNCLCC. Two search engines were also searched (Google and Journalservice for medics) with the same keywords than mentioned earlier.

Finally a search for systematic reviews in the Cochrane database and in DARE (4 references) was performed.

3.6.2.2 *Selection*

The guidelines on diagnosis, treatment and follow up of testicular cancer were reviewed. In order to exclude all opinions papers or narrative reviews, the guidelines with no mention of a clear evidence-based system to grade the recommendations, were excluded. The guidelines were selected and appraised by two experts, using the AGREE instrument. All disagreements were resolved by consensus. The results of the appraisal are presented in appendix 1. The guidelines with an overall assessment of “strongly recommended” or “recommended” were selected and used to develop a synthesis which was discussed and reviewed by the expert appointed by the working party of the College of Oncology, in order to adapt the recommendations to the Belgian situation. A special interest was brought to the methods used in all the reviewed guidelines to search and select the evidence (databases, search strategies, selection criteria, selection methods). The synthesis was build using the guidelines rated as “strongly recommended” as basis. For every point, the recommendations of the guidelines rated “recommended with provisos”, if any, were also cited. In case of disagreement between different guidelines, the recommendations of the guidelines rated “strongly recommended” were always preferred on the others. For specific points for which no recommendations were found in the “strongly recommended” guidelines, the evidence of “recommended guidelines” or coming from good systematic reviews have been used.

3.6.2.3 Grading of recommendations

Each guideline developer has his own evidence grading system. To synthesize the different systems, a correspondence table is presented hereunder. The key to evidence statements and grades of recommendations used in the selected guidelines are presented in the appendices.

KCE grade	SIGN	NICE	ASCO	NCI	NCCN	EGCCCG	EAU
A	A	A	A	I		IA & IB	A
B	B & C	B	B	2 & 3i & 3ii		IIA & IIB	B
C	D	C	C & D	3iii	I & 2A	III & IV	

A = Evidence derived from RCT or meta-analysis or systematic review of RCT.

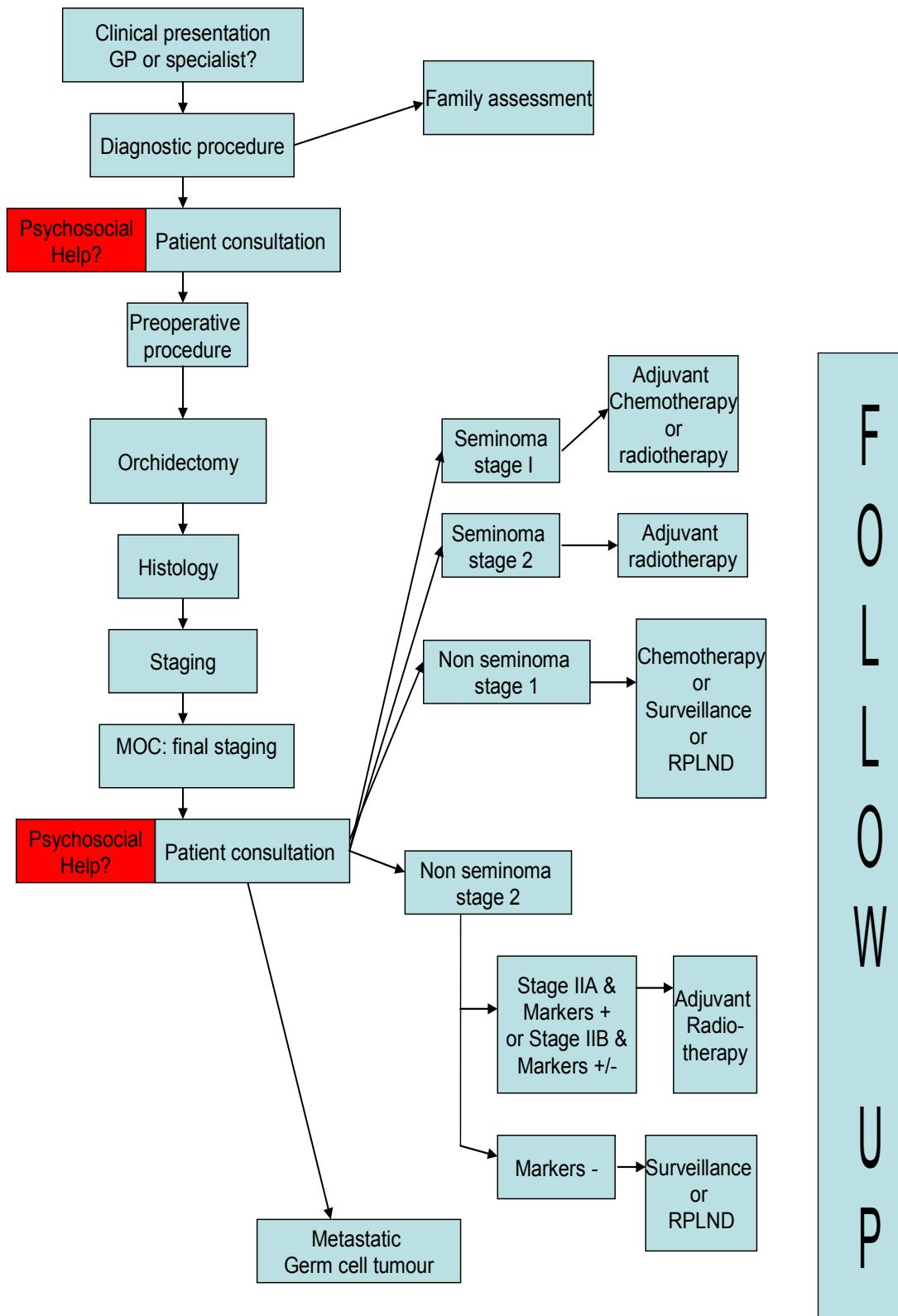
B = Evidence from non-randomised controlled trials or observational studies.

C = Professional consensus, or case reports, case series.

For presentation reasons, grade A recommendations, with a very high level of evidence, are put in bold letter; grade B recommendations with a high level of evidence are put in normal letters and grade C recommendations, principally based on consensus are put in italic letters. Due to their weak level of evidence, these last recommendations could be changed in a near future depending on the body of evidence. Nevertheless they are presented in this work because they are based on a large consensus within the scientific community.

3.6.3 Testicular cancer guideline

3.6.3.1 GENERAL ALGORITHM



Introduction

The guidelines presented covers diagnosis, treatment and follow up of testicular cancer. It is based on the existing international guidelines which have been critically appraised (see Appendices I) and on the consensus of national societies.

We will go through the following topics:

- diagnosis
- clinical staging
- first multidisciplinary team meeting
- surgical procedure
- histological procedure
- final staging (2d MDT meeting)
- treatment
- follow up

The grade of recommendation is stated in the text as follow:

GR A = Evidence derived from RCT or meta-analysis or systematic review of RCT

GR B = Evidence from non-randomised controlled trials or observational studies

GR C = Professional consensus, or case reports or case series

I. Diagnosis

Patient's history

A *personal*/history has to be taken.

The diagnostic procedure is generally indicated for patients with the following symptoms: swelling, pain, sensation of scrotal heaviness[57] (**GR B**). The clinical presentation is typically a young man with testicular mass and/or pain in the back[58]/(**GR C**). In a minority of patients, the clinical presentation is extra gonadal (retroperitoneal or mediastinal)[57-61] (**GR C**).

The following elements have to be detected: undescended testis, early age of puberty and sedentary life style [59], and contralateral testis tumour [57-61] (**GR B**).

A *family* history has to be taken: testicular tumour in any first grade relative? [58, 60, 61] (**GR B**).

Examination: palpation [58]. Physical examination may be sufficient for the diagnosis of testicular cancer [61] (**GR B**).

Markers: Feto-Protein and -HCG for distinction between seminoma and non seminoma [61] [57] [58, 60] (**GR B**) and for the follow up of patients with teratoma [57] (**GR B**).

In case of advanced disease: LDH in addition, as prognostic factor [61] [57] (**GR B**).

Imaging: Testicular sonography (7.5 MHz transducer) [58] [61] [57] (**GR B**) except if clinically evident [57] (**GR B**).

Biopsy: in case of symptoms with no elevation of markers [61] [57] and for contralateral testis (open or needle biopsy)[57, 58] (**GR B**).

The biopsy must give answers to the following questions:

- Presence or absence of Carcinoma in situ (**GR C**)
- Degree of spermatogenesis (**GR C**)
- Evidence of atrophy of seminiferous tubules [57] (**GR B**).

2. Clinical staging:

To detect metastases, the following examinations are recommended:

Imaging

CT scan of abdomen and pelvis [57] [60] (**GR B**)

Chest CT scan except for seminoma stage I [57, 60, 61] (**GR B**)

MRI of chest and abdomen if CT contraindicated, (**GR C**)

CT scan or preferably MRI of CNS: only in advanced disease with intermediate or poor prognosis, or if symptoms (**GR C**)

PET scan: cfr HTA report of KCE
<http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf> :

Staging: Due to the difficulties for classical imaging techniques to evaluate small volume metastasis, every patient receives chemotherapy or radiotherapy (or retroperitoneal lymph nodes resection) but this is not needed in 70% of patients with non germ cell tumour and in 80% of patients with germ cell tumour. Nevertheless, the sensitivity of PET between 70% and 90% with specificity between 94% and 100% is not high enough to diminish the value of adjuvant therapies in case of negative results. Indeed the risk of a false negative result for nodes smaller than 1 cm is too high.

cTNM: pre-treatment clinical classification, based on clinical examination, imaging, biopsy, (TNM classification for testicular cancer UICC, 2002 Sixth Edition) [61].

N Regional Lymph Nodes clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

3. First Multidisciplinary Team Meeting (MOC)

The objective of this first meeting is to decide if the cancer is metastatic or not and to decide on the related therapeutic options (**GR C**).

If possible, the general practitioner of the patient should attend this meeting. If not, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient (**GR C**).

Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision [57] (**GR B**).

The fertility issues must be discussed with the patient: sperm banking, testosterone replacement and contraception [57] (**GR B**)

Information about local support services should be made available to both the patient and their relatives. Healthcare professionals should respect patients' wishes to be involved when making plans about their own management (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started [57] (**GR C**).

4.a Surgical procedure

The patient is always oriented to surgery (inguinal orchidectomy) which remains the only curative option [57, 58, 60, 61] (**GR B**). There is no need for emergency surgery [58] (**GR C**).

A preoperative risk assessment should be performed according to the appropriate guidelines (see <http://www.kenniscentrum.fgov.be/fr/Publications.html>).

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics, and immediate orchidectomy with division of the spermatic cord at the internal inguinal ring has to be performed if a tumour is found [57, 58, 60, 61] (**GR B**).

If the diagnosis is not clear, a testicular biopsy is taken for frozen section histological examination. Once the diagnosis of testicular tumour has been established, the testis is enveloped into the sponges which protected the surgical field, gloves are changed, the inguinal channel is opened and the spermatic cord is divided at the level of the internal ring. The specimen is sent for definitive histology [57, 58, 60, 61] (**GR B**).

It must be explained to patients preoperatively that this procedure is being done to exclude any cancer in a situation where there is high index of suspicion and that following such a bivalving procedure in those situations where malignancy is not confirmed and where the testis is replaced there may be moderate to severe testicular damage [57] (**GR C**).

It is said that in case of disseminated disease and life-threatening metastases, up-front chemotherapy can be started and orchidectomy delayed until clinical stabilisation [61] (**GR C**).

From time to time a scrotal exploration is performed for what is thought to be an inflammatory non malignant condition but tumour is found and it is necessary to proceed to orchidectomy. In this situation there is no need to perform secondary wound excision and the postoperative management should continue in exactly the same way as if the operation had been performed through the conventional inguinal approach [57] (**GR B**).

A testicular prosthesis should be offered to all patients [57] (**GR B**).

4.b Histological procedure

After surgical ablation of the testis, pathological assessment is mandatory and determination of serum tumour markers is advisable [61] (**GR B**).

Mandatory pathological requirements [58] (**GR C**):

- Macroscopic features: side, testis size, tumoural maximum size and macroscopic features of epididymis, spermatic cord and tunica vaginalis [57] (**GR C**).
- Sampling: 1 cm² section for every cm of maximal tumoural diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area (**GR C**).
- Microscopic features and diagnosis [57]: histological type (specify individual components and estimate amount as percentage) (**GR C**).
- presence or absence of peri-tumoral venous and/or lymphatic invasion [60] (**GR B**).
- *presence or absence of albuginea, tunica vaginalis, epididymis or spermatic cord invasion (GR C)*.
- presence or absence of intratubular germinal neoplasia (Tin) in non-tumoural parenchyma (**GR C**).
- Category pT category according to TNM 2002.
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and beta-hCG [60] (**GR B**).
- Advisable immunohistochemical markers
- In seminoma: cytokeratins (CAM 5.2), PLAP
- In intratubular germ cell neoplasia: PLAP
- Other advisable markers: Chromogranine A (Cg A), Ki 1, and NSE [61] (**GR C**)

The histological report must contain the following items:

- Localisation
- multiplicity
- Gross Description: Size of Testis, Size of Tumour,
- Features: Haemorrhage, Necrosis, Cysts
- Number of blocks of tumour taken
- Germ Cell Tumour Components (WHO descriptive terms)

Seminoma (presence of syncitiotrophoblasts), NSGCT (Differentiated somatic elements, Embryonal Carcinoma, Syncytiotrophoblast, Yolk Sac Tumour, Choriocarcinoma, Other)

- Other tumour type
- Invasion: Vascular space invasion, cut end of cord, confined to testis, invades rete, invades tunica albuginea, invades epididymis, present in cord, invades scrotum
- Other features: areas of scarring only, biopsy of contralateral testis? Intra Tubular Germ Cell Neoplasia present?

- Summary (BTTP diagnosis): Seminoma, Spermatocytic Seminoma, Combined Tumour, Other, TD, MTI, MTU, MTT (NHS National minimum dataset Testicular cancer histopathology report) (**GR C**).

The tumour must be classified according to the WHO [58] (**GR C**).

WHO classification of germ cell tumours of the testis:

Tumours of one histological type

- Seminoma
- Spermatocytic seminoma
- Embryonal carcinoma
- Polyembryoma
- Teratoma: Mature, immature, with malignant transformation
- Yolk sac tumour (endodermal sinus tumour)
- Choriocarcinoma

Tumours of more than one histological type

- Embryonal carcinoma with teratoma (teratocarcinoma)
- Choriocarcinoma and any other types (specify)
- Other combinations (specify)

4.c Final Staging

Testicular cancers should be staged using the TNM staging system:

pTNM: post-surgical histopathological classification.

TNM classification for testicular cancer (UICC, 2002 Sixth Edition) [61] [57]

pT Primary Tumour	
PTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour (e.g., histologic scar in testis)
PTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion:tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
pN Pathological	
PNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pNI	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s) or lung
M1b	Other sites

TNM Stage grouping

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT /TX	N0	M0	SI-3
Stage II	Any pT /TX	N1-3	M0	SX
Stage II A	Any pT /TX	N1	M0	S0
	Any pT /TX	N1	M0	SI
Stage II B	Any pT /TX	N2	M0	S0
	Any pT /TX	N2	M0	SI
Stage IIC	Any pT /TX	N3	M0	S0
	Any pT /TX	N3	M0	SI
Stage III	Any pT /TX	Any N	M1	SX
Stage IIIA	Any pT /TX	Any N	M1a	S0
	Any pT /TX	Any N	M1a	SI
Stage IIIB	Any pT /TX	N1-3	M0	S2
	Any pT /TX	Any N	M1a	S2
Stage IIIC	Any pT /TX	N1-3	M1a	S3
	Any pT /TX	Any N	M1b	S3

The staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports (**GR C**).

If possible, the general practitioner of the patient should attend this meeting. If not, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient (**GR C**).

Depending on tumour stage, the further treatment options are decided:

The adjuvant chemotherapy regimen is decided during the multidisciplinary team meeting. A written report with staging and treatment options is mandatory for each patient (**GR C**).

5. Treatment

A. Seminoma CS I

There are three main options to treat a Seminoma stage I:

The decision must be based on a discussion with the patient, taking into account the benefits and disadvantages of each strategy as well as the individual situation (**GR C**).

Adjuvant radiotherapy of retroperitoneal para-aortic lymphatic field with a total target volume of 20 Gy with modern radiotherapy (linear accelerator) [58], [61], [57] (**GR B**). This is the standard treatment for Stage I T1 to T3 patients with undisturbed lymphatic drainage [61] (**GR C**).

The dose is applied in single doses of 2 Gy, five fractions per week [58], [57] (GRB). The upper field margin is defined by D11 and the lower field margin by L5. The lateral field should include the ipsilateral renal hilum and the contralateral processus transversus of the lumbar vertebrae [58] [57] (GR A).

Surveillance is also an option due to the fact that 20 % of patients only relapse after orchidectomy, and due to the potential risk of subsequent cancer following radiotherapy [58, 61] (GR C). This strategy is not valid in case of doubt about patient's compliance [57] (GR B) and must take into account the greater psychological stress due to higher risk of relapse [58] (GR C). On the contrary this strategy may be recommended for patients with horseshoe or pelvic kidney, inflammatory bowel disease or prior radiotherapy [62] (GR C).

The risk factors for relapse are a tumour size > 4 cms and invasion of rete testis. Surveillance requires a prolonged and more intensive follow-up (repeated imaging examination of the retroperitoneal nodes for at least 5 years after orchidectomy) [58, 61] (GR B). In case of relapse, a more intensive treatment is needed [58] but with equivalent results to the adjuvant radiotherapy [58, 61] (GR C).

Adjuvant carboplatin chemotherapy with one cycle of carboplatin AUC7 (7X [glomerular filtration rate + 25] mg). This strategy may reduce the occurrence of second primary testicular germ-cell tumours following radiotherapy. However, the findings need to be confirmed [63] (GR C)..

The relapse rate is the same for chemotherapy and for radiation therapy but with other localisation (more retroperitoneal lymph node relapse with chemotherapy >< more pelvic lymph node relapse with irradiation) [58, 61] (GR A).

A decision tree is presented in appendix 6

B. Seminoma CS II A and B

The standard treatment is radiotherapy [57] (GR B).

Target volume includes the paraaortal and ipsilateral iliacal lymphatics [58] [57](GR B).

Upper field margin: upper border of D11 [58] [57] (GR B)

Lower field margin: upper border of the acetabulum [57] (GR B)

Lateral field: for CS IIA, the same than for CSI [57] (GR B); for CS IIB, lateral field margins are individually modified according to the extension of the lymph nodes with a safety margin of 1 – 1.5 cm [58] (GR B).

Radiation doses: 30 Gy for CSIIA and 36 Gy for CSIIB, homogeneously with single dose of 2 Gy at five fractions per week [58] (GR C).

Shielding of the remaining testicle is mandatory [58] (GR C).

3 months after radiation therapy, abdominal and pelvic CT should be performed (basis for follow up) [58] (GR B).

An alternative strategy for patients not willing radiotherapy is 3 cycles BEP or 4 cycles PE [58] [61] (GR B).

BEP and PE regimens (every 3(4) weeks)

- BEP: Cisplatin 20mg/m², days 1-5 and hydratation
- Etoposide : 120mg/m², days 1,3,5
- Bleomycin : 30mg, days 2,9,16
- PE: etoposide 100mg/m², days 1-5

Availability and reimbursement policy of the chemotherapy regimens in Belgium may be checked at: (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm)
http://www.bcfi.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm)

A decision tree is presented in appendix 6

C. Non Seminoma CS I

The most important prognosis factor for relapse is vascular invasion.

In case of low risk (no vascular invasion), the standard treatment is follow up [57] [58] (**GR B**). In case of relapse, a chemotherapy treatment will result in a cure rate close to 100% [57, 58] (**GR B**).

In case of high risk (vascular invasion), the standard treatment is 2 cycles of BEP. For several reasons like patient choice, surveillance only may be an option, with a cure rate > 98% in case of relapse cured by chemotherapy [57, 58] (**GR B**).

In both cases, a third option is possible: nerve sparing lymphadenectomy, with a risk of recurrence or relapse of +/- 10% [58] (**GR C**).

A decision tree is presented in appendix 6.

D. Non Seminoma CS II A & B

Patients with abnormal serum tumour markers AFP/HCG and/or LDH are treated depending of the prognosis (see prognosis table of the IGCCCG in appendix 4).

In case of good prognosis, 3 cycles of BEP and if Bleomycin is contraindicated, 4 cycles of Carboplatin and Etoposide (PE) can be given [58] (**GR A**).

Patients with retro-peritoneal lymph nodes (I-2 cms) suspected to be CS IIA without tumour markers: either:

Staging and nerve sparing Retro Peritoneal Lymph Nodes Dissection [58] (**GR C**). If pathology stage is I, surveillance is recommended [58] (**GR B**). If pathology stage is II A or B, surveillance or 2 cycles BEP [58] (**GR A**); or

Surveillance with a follow up at short intervals (6 weeks) [58] (**GR C**): if regression of the tumour, surveillance [58] (**GR C**); if no change or progression of the disease with negative markers RPLND or surveillance [58] (**GR C**); if progression of the disease with positive markers, 3 cycles BEP and resection of the residual tumour [57, 58] (**GR B**).

A decision tree is presented in appendix 6.

E. Advanced disease:

For patients with advanced disease, treatment is based on the prognosis evaluation, according to IGCCCG criteria (see table in appendix 7).

For patients with good prognosis disease, standard treatment is 3 cycles of BEP. In case of contraindication of bleomycin, 4 cycles of cisplatin and etoposide(PE) [58] (**GR A**).

For intermediate and poor prognosis patients, the 5 day BEP regimen for four cycles is the standard treatment. [58] (**GR A**).

For intermediate prognosis patients, the treatment is given in prospective trials to design more effective treatments [58] (**GR C**).

For brain metastases, resection if the metastases are accessible, followed by curative or palliative radiotherapy [57] (**GR C**) in addition to systemic chemotherapy [58] (**GR C**).

Patients with seminoma who have residual masses following chemotherapy can generally be managed by surveillance. Surgery is not routinely indicated [57, 58] (**GR B**)

Cisplatin based salvage chemotherapy is indicated after first line therapy with BEP: 4 cycles of Cisplatin, etoposide and ifosfamide (PEI), etoposide, ifosfamide and cisplatin (VIP) or vinblastine, ifosfamide and cisplatin (VEIP) or paclitaxel, ifosfamide and cisplatin (TIP) [58] (**GRB**).

For the treatment of late relapse, surgery should be considered [57] (**GRB**).

A decision tree is presented in appendix 6 and the chemotherapy regimens in appendices 8.

F. Management of unresectable metastases:

Each patient should receive an evaluation for first and second line chemotherapy. The most important parameter therefore is the health performance status (**GR C**).

The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed (**GR C**).

The need for a psychosocial help must be evaluated and, if required, the help has to be started (**GR C**).

Patients with advanced cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management (**GR C**).

Palliative care specialists should be members of, and integrated with, cancer multidisciplinary teams; their role includes the provision of education and advice for other health professionals and direct patient management (**GR C**).

A patient in good health status and progressing despite standard therapy should be proposed a clinical trial protocol (**GR C**).

6. Follow up

Large differences exist in the risk of recurrence or progression for patients with germ cell cancer due to differences in stage at initial presentation and individual management decisions. The intensity of the follow up depends on these factors. There is limited information about the optimal follow up procedure [58] (**GR C**).

Early identification of therapeutic failure in Non seminomatous Germ cell tumours by assessing serum tumour markers decline during chemotherapy is still not ready for routine clinical use [64].

PET scan: cfr HTA report of KCE
<http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf>

For residual mass evaluation, there is evidence of diagnosis accuracy, but no evidence that PET scan results change the patient management.

For therapeutic response and detection of occult recurrence, there is a lack of evidence for the use of PET

3.6.4 Quality control

The good utilization of a guideline has to be evaluated. Therefore, a guideline has to be accompanied with quality control criteria.

These criteria should at least assess the following steps of the algorithm:

- clinical staging process
- surgery process
- histology process
- adjuvant chemotherapy and other treatments

For each step, quality indicators will be developed in a further step alongside with clinical pathways. The development of quality indicators for cancer is part of the KCE research programme.

4 INFORMATISATION OF THE COLORECTAL CANCER GUIDELINE

The initial goal of this project was the development of an online publication tool for guidelines in oncology. This tool was to be user-friendly, interactive, reachable on the web and eventually usable as a decision support system.

The first step of the project was the translation of the texts of the targeted guidelines in an electronic format understandable by computers. The modelling language PROforma was retained as the format to express computerized guidelines. The translation has consisted in an iterative process of semantic analysis of the text, conceptual modelling using the abstract objects defined by PROforma (enquiries, actions, decisions and plans) as well as careful and extensive testing of the obtained models.

At the same time, several meetings with the working group of the College of Oncology were organized. These meetings allowed the definition of the functional requirements of the "portal", a web application usable to publish and consult the guidelines in the form of interactive sessions. These requirements were formalized and approved in a document entitled « Mise en ligne du guideline « cancer colorectal» Expression des besoins fonctionnels ».

The developments of the portal were realized during a period of approximately one month and a half.

Outlined briefly, the portal is constituted of the following components:

- A graphical user interface, usable on the web, which allows the users to interact with the published guidelines;
- A database storing the administrative data related to the users, the published guidelines and the usage sessions of guidelines started by the users;
- A guideline interpreter, implementing the PROforma specification;
- The implementation of the administrative logic of the portal.

After this first development phase, a prototype of the application was put in line with the aim of testing. At the end of this period of test, it was decided to adopt a mixed representation of the guidelines:

- A detailed interactive presentation, based on PROforma and thus being able to be used as a computerized decision-making system;
- A simplified presentation, based on conceptual maps, which makes it possible to navigate quickly in a guideline.

Conceptual Maps are simple and practical knowledge representation tools that allow conveying complex conceptual messages in a clear, understandable way. They are represented naturally as graphs. This form of representation is particularly well adapted to the graphical representation of guidelines. Moreover, the guidelines generally comprise a graphical chart of their algorithm.

To carry out the representation based on conceptual maps, we chose to use the CmapTools developed by the Institute for Human and Machine Cognition associated to the West Florida University (USA). This is a freely downloadable tool, very versatile and easy to use.

The client-server architecture of CmapTools and its sophisticated network model allow easy publishing of the knowledge models of guidelines in concept map servers (CmapServers), and enables concept maps to be linked to related concept maps and to other types of media (e.g., images, videos, web pages, etc.) in other servers. The collaboration features enable remote users to asynchronously and/or synchronously

collaborate in the construction of concept maps, and promote comments, criticism, and peer review.

The complete process of development, the search for foreign experiments in the literature and a presentation of the lay out of the website are presented in appendices 9 to 11.

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6 APPENDICES

APPENDIX I: EVIDENCE TABLE COLORECTAL GUIDELINES

Titel	Country	Year	Scope	AGREE overall assessment
Management of colorectal cancer – SIGN [23]	Scotland	2003	Colorectal	Strongly recommend
Guidance on Cancer Services Improving Outcomes in Colorectal Cancer - NICE[24]	UK	2003	Colorectal	Strongly recommend
Guidelines for the management of colorectal cancer - The association of coloproctology of GB and Ireland[30]	UK	2001	Colorectal	Recommend (with provisos or alterations)
Adjuvant therapy for Stage II & III Colon Cancer Following Complete resection – Cancer care Ontario [37]	Canada	2000	Colon	Strongly recommend
Use of irinotecan in treatment of metastatic colorectal carcinoma - Cancer care Ontario[47]	Canada	2000	Colorectal	Strongly recommend
Use of raltitrexed in management of metastatic colorectal cancer - Cancer care Ontario [48]	Canada	2002	Colorectal	Strongly recommend
Use of Irinotecan combined with 5Fluorouracil and leucovirin as first line therapy for metastatic colorectal cancer - Cancer care Ontario[49]	Canada	2003	Colorectal	Strongly recommend
Follow up of patients with curatively resected	Canada	2004	Colorectal	Strongly recommend

Titel	Country	Year	Scope	AGREE overall assessment
colorectal cancer – Cancer care Ontario [39]				
Postoperative adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II & III Rectal Cancer – Cancer care Ontario[56]	Canada	2001	Rectum	Strongly recommend
The use of Preoperative radiotherapy in the management of patients with Clinically respectable Rectal cancer - Cancer care Ontario[53]	Canada	2004	Rectum	Strongly recommend
Colon Cancer – NCCN[28]	USA	2004	Colon	Recommend (with provisos or alterations)
Rectal Cancer - NCCN [28]	USA	2004	Rectum	Recommend (with provisos or alterations)
Colon cancer treatment – NCI[27]	USA	2004	Colon	Recommend (with provisos or alterations)
Rectal cancer treatment – NCI[52]	USA	2003	Rectum	Recommend (with provisos or alterations)
Colorectal cancer surveillance et Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [35]	USA	2000	Colorectal	Strongly recommend
Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [36]	USA	2004	Colon	Strongly recommend
Colorectal cancer MOH Clinical practice guidelines[33]	Singapore	2004	Colorectal	Recommend (with provisos or alterations)
Coloncarcinoom - Oncoline (vereniging van Integrale kankercentra) :	Netherlands	2000	Colon	Would not recommend

Titel	Country	Year	Scope	AGREE overall assessment
consensus based[65]				
Rectumcarcinoom – Oncoline (vereniging van Integrale kankercentra) : consensus based[66]	Netherlands	2001	Rectum	Would not recommend

COLORECTAL CANCER AGREE

Key items	SIGN	NICE	NCCN	NCI	Singapore MOH	Assoc Coloproct GB	Cancer Care Ontario	ASCO	Oncoline
Scope and Purpose									
1	4	4	4	4	4	4	4	4	4
2	4	4	4	4	4	4	4	4	4
3	4	4	4	4	4	4	3	4	4
Stakeholder involvement									
4	4	4	4	1	4	4	3	1	2
5	3	3	1	3	1	4	3	1	1
6	4	4	3	4	4	4	4	4	4
7	2	2	2	2	1	2	2	2	2
Rigour of development									
8	4	4	2	2	1	1	4	4	1
9	4	4	4	4	4	4	4	4	1
10	4	4	4	4	1	4	4	4	1
11	4	4	4	4	4	4	4	4	1
12	4	4	4	4	4	4	4	4	1
13	4	4	2	2	1	2	4	2	1
14	4	3	3	1	4	1	4	4	1
Clarity and Presentation									
15	4	4	4	4	4	4	4	4	4
16	4	4	4	4	4	4	4	4	4
17	4	4	4	4	4	4	4	3	4
18	4	2	4	4	4	2	2	1	1

COLORECTAL CANCER AGREE

Key items	SIGN	NICE	NCCN	NCI	Singapore MOH	Assoc Coloproct GB	Cancer Care Ontario	ASCO	Oncoline
Applicability									
19	2	1	1	1	1	1	1	1	1
20	1	4	1	1	1	1	1	1	1
21	4	4	1	1	1	1	1	1	1
Editorial independence									
22	4	4	4	2	1	4	4	4	4
23	4	4	2	2	1	1	4	1	1
Overall assessment	SR	SR	R	R	R	R	SR	SR	NR

The assessment of the guidelines was made with the AGREE instrument.

All details can be found on the AGREE collaboration website:

<http://www.agreecollaboration.org/>

The AGREE instrument can be found on: <http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf>

APPENDIX 2: KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS COLORECTAL GUIDELINE

SCOTTISH INTERCOLLEGiate GUIDELINES NETWORK (SIGN)

Levels of evidence

- I⁺⁺ High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
- I⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- I⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non analytic studies, e.g. case reports, case series
- 4 Expert opinion

Grades of recommendation

- A At least one meta-analysis, systematic review of RCTs, or RCT rated as I⁺⁺ and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as I⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as I⁺⁺ or I⁺
- C A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE)

- A Evidence derived from randomised controlled trials or systematic reviews of randomised trials
- B Evidence from non-randomised controlled trials or observational studies
- C professional consensus

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Level

- I Meta-analysis of multiple well designed, controlled studies; randomised trials with low false-positive and low false-negative errors (high power)
- II At least one well designed experimental study; randomised trials with high false-positive or high false-negative errors or both (low power)
- III Well designed, quasi-experimental studies, such as nonrandomised controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series
- IV Well designed, non experimental studies such as comparative and correlational descriptive and case studies
- V Case reports and clinical examples

Grade

- A Evidence of type I or consistent findings from multiple studies of type II, III or IV
- B Evidence of type II, III or IV and generally consistent findings
- C Evidence of type II, III or IV but inconsistent findings
- D Little or no systematic empirical evidence

NATIONAL CANCER INSTITUTE (NCI)

Strength of study design

- Randomised controlled clinical trials
- Double-blinded
- Non blinded (allocation schema or treatment delivery)
- Non randomised controlled clinical trials
- case series
- Population-based, consecutive series
- Consecutive cases (not population-based)
- Non consecutive cases

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

Category I	There is uniform NCCN consensus, based on high level evidence, that the recommendation is appropriate
Category 2A	there is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate
Category 2B	There is non uniform consensus (but no major disagreement), based on lower level evidence including clinical experience, that the recommendation is appropriate
Category 3	There is major NCCN disagreement that the recommendation is appropriate

SINGAPORE MINISTRY OF HEALTH (SMOH)

Levels of evidence

- Ia Evidence obtained from meta-analysis of RCTs
- Ib Evidence obtained from at least one RCT
- Ila Evidence obtained from at least one well designed controlled study without randomisation
- IIb Evidence obtained from at least one other type of well designed quasi-experimental study
- III Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Grades

- A Requires at least one RCT, as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (evidence levels Ia and Ib)
- B Requires availability of well conducted clinical studies, but no RCT on the topic of recommendation (evidence levels IIa, IIb, III)
- C Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality (evidence level IV)

APPENDIX 3: VARIOUS CHEMOTHERAPY REGIMENS

CHEMOTHERAPY REGIMENS	
FOLFOX	
FOLFOX 4	Irinotecan 125 mg/m IV over 90 minutes, days 1, 8, 15, 22 Leucovorin 20 mg/m IV, days 1, 8, 15, 22 5-FU 500 mg/m IV, days 1, 8, 15, 22 Repeat every 6 weeks
Oxaliplatin 85 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours, days 1 and 2 5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours continuous infusion, days 1 and 2 Repeat every 2 weeks	Capecitabine 13 2,500 mg/m /day PO in two divided doses, days 1-14, followed by 7 days rest Repeat every 3 weeks
FOLFOX 6	Bolus or infusional 5-FU/leucovorin Mayo regimen Leucovorin 20 mg/m IV bolus, days 1-5 5-FU 425 mg/m IV bolus one hour after start of Leucovorin, days 1-5 Repeat every 4 weeks
Oxaliplatin 100 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours, day 1 5-FU 400 mg/m IV bolus, then 2.4-3.0 g/m IV over 46 hours continuous infusion Repeat every 2 weeks	Roswell-Park regimen Leucovorin 500 mg/m IV over 2 hours, days 1, 8, 15, 22, 29, and 36 5-FU 500 mg/m IV bolus 1 hour after start of Leucovorin, days 1, 8, 15, 22, 29, 36 Repeat every 6 weeks
FOLFOX 7	de Gramont Leucovorin* 400 mg/m IV over 2 hours, days 1 and 2 5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours continuous infusion, days 1 and 2 Repeat every 2 weeks
FOLFIRI	Protracted IV 5-FU 5-FU 300 mg/m /d protracted IV infusion
Irinotecan 180 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours prior to 5-FU, days 1 and 2 5-FU 400 mg/m IV bolus, then 600mg/ m IV over 22	Irinotecan Irinotecan 125 mg/m IV over 90 minutes, days 1, 8,

hours	15, 22
continuous infusion, days 1 and 2	Repeat every 6 weeks
Repeat every 2 weeks	Irinotecan 300-350 mg/m IV over 90 minutes, day 1
Irinotecan 180 mg/m IV over 90 minutes, day 1	Repeat every 3 weeks
Leucovorin 400 mg/m IV over 2-hour infusion during Irinotecan, day 1	Cetuximab ± irinotecan
5-FU 400 mg/m IV bolus, then 2.4-3 g/m IV over 46 hours	Cetuximab 400 mg/m 1st infusion, then 250 mg/m weekly
continuous infusion	±
Repeat every 2 weeks	Irinotecan
Bevacizumab + 5-FU containing regimens:	350 mg/m IV every 3 weeks
Bevacizumab 5mg/kg IV every 2 weeks + 5-FU and Leucovorin	or
or IFL	180 mg/m IV every 2 weeks
or FOLFOX	or
or FOLFIRI	125 mg/m every week for 4 weeks
IFL In combination with bevacizumab	Every 6 weeks

APPENDIX 4: EVIDENCE TABLE TESTICULAR GUIDELINES

Title	Country	Year	Scope	AGREE overall assessment
SIGN: Management of adult testicular germ cell tumours[57]	UK Scotland	1998 and update 2005	Testicular germ cell tumours	Strongly recommend
NICE: Improving outcomes in urological cancers [59]	UK	2002	Urological cancers	Recommend (with provisos or alterations)
The Royal College of radiologists COIN guidelines: Testicular Germ cell Tumours[60]	UK	1998	Testicular germ cell tumours	Recommend (with provisos or alterations)
European Association of Urology: Guidelines on Testicular Cancer[61]	Europe	2004	Testicular germ cell tumours	Recommend (with provisos or alterations)
European Consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group[58]	Europe	2004	Testicular germ cell tumours	Recommend (with provisos or alterations)
NCCN: Testicular cancer[62]		2005	Testicular germ cell tumours	Recommend (with provisos or alterations)
National Cancer Institute: Testicular cancer Treatment[67]	USA	2003	Testicular germ cell tumours	Recommend (with provisos or alterations)
Cancercare Ontario Program: Surveillance programs for early stage non-seminomatous testicular cancer[68]	Canada	2001	Non seminomatous testicular cancer	Recommend (with provisos or alterations)
Vereniging van Integrale Kankercentra: Testiscarcinoom[69]	The Netherland	2002	Testicular germ cell tumours	Not recommend

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The AGREE instrument can be found on:
<http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf>

TESTICULAR CANCER GUIDELINES: AGREE scores

TESTICULAR CANCER GUIDELINES: AGREE scores

APPENDIX 5 KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS TESTICULAR GUIDELINE

SCOTTISH INTERCOLLEGiate GUIDELINES NETWORK (SIGN)[57]

Levels of evidence

- I⁺⁺ High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
- I⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- I⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
- High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non analytic studies, e.g. case reports, case series
- 4 Expert opinion

Grades of recommendation

- A At least one meta-analysis, systematic review of RCTs, or RCT rated as I⁺⁺ and directly applicable to the target population; or
- A body of evidence consisting principally of studies rated as I⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as I⁺⁺ or I⁺
- C A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE)

- A Evidence derived from randomised controlled trials or systematic reviews of randomised trials
- B Evidence from non-randomised controlled trials or observational studies
- C professional consensus

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Level

- I Meta-analysis of multiple well designed, controlled studies; randomised trials with low false-positive and low false-negative errors (high power)
- II At least one well designed experimental study; randomised trials with high false-positive or high false-negative errors or both (low power)
- III Well designed, quasi-experimental studies, such as nonrandomised controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series
- IV Well designed, non experimental studies such as comparative and correlational descriptive and case studies
- V Case reports and clinical examples

Grade

- A Evidence of type I or consistent findings from multiple studies of type II, III or IV
- B Evidence of type II, III or IV and generally consistent findings
- C Evidence of type II, III or IV but inconsistent findings
- D Little or no systematic empirical evidence

NATIONAL CANCER INSTITUTE (NCI)

STRENGTH OF STUDY DESIGN

- Randomised controlled clinical trials
- Double-blinded
- Non blinded (allocation schema or treatment delivery)
- Non randomised controlled clinical trials
- case series
- Population-based, consecutive series
- Consecutive cases (not population-based)
- Non consecutive cases

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)[62]

Category I	There is uniform NCCN consensus, based on high level evidence, that the recommendation is appropriate
Category 2A	there is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate
Category 2B	There is non uniform consensus (but no major disagreement), based on lower level evidence including clinical experience, that the recommendation is appropriate
Category 3	There is major NCCN disagreement that the recommendation is appropriate

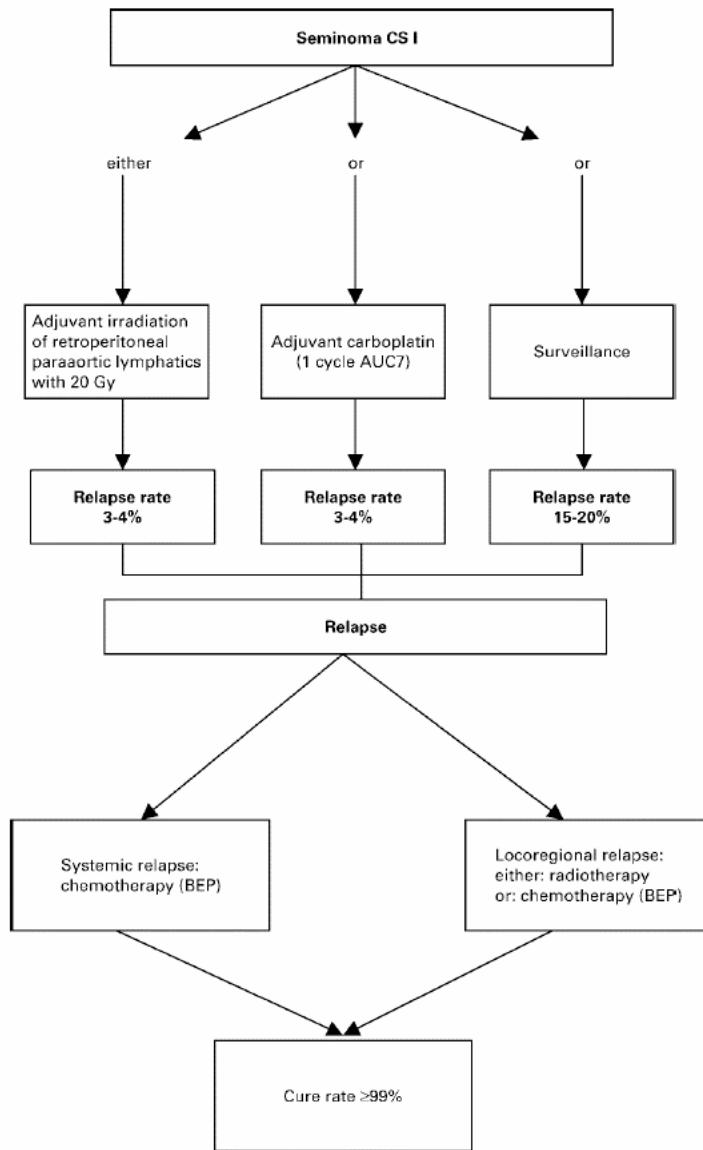
European Association of Urology (see AHRQ)[61]

European Consensus on diagnosis and treatment of germ cell cancer [58]

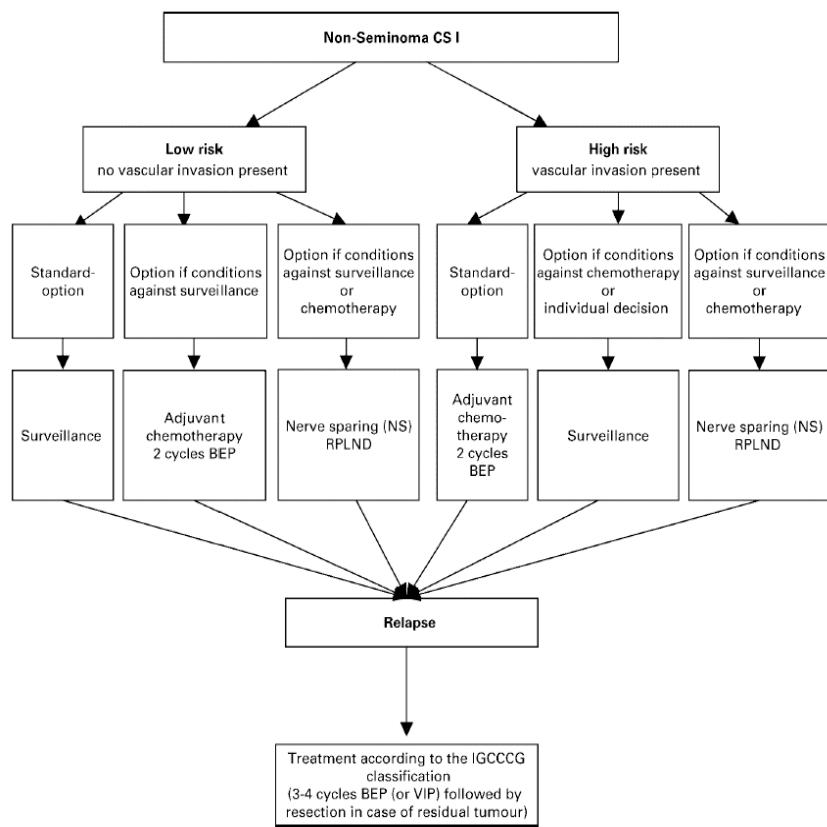
Level IA	Evidence obtained from meta-analysis of RCT and systematic reviews of RCT
Level IB	Evidence obtained from at least one RCT
Level IIA	Evidence obtained from at least one well-designed controlled study without randomisation
Level IIB	Evidence obtained from at least one other type of well-designed quasi-experimental study
Level III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
Level IV	Evidence obtained from expert committee or opinion and/or clinical experience of respected authorities without transparent proof.

APPENDIX 6 : TREATMENT DECISION TREES

Treatment algorithm after orchiectomy according to individual risk factors in patients with seminoma CS I, taken from EGCCCG guideline [58]

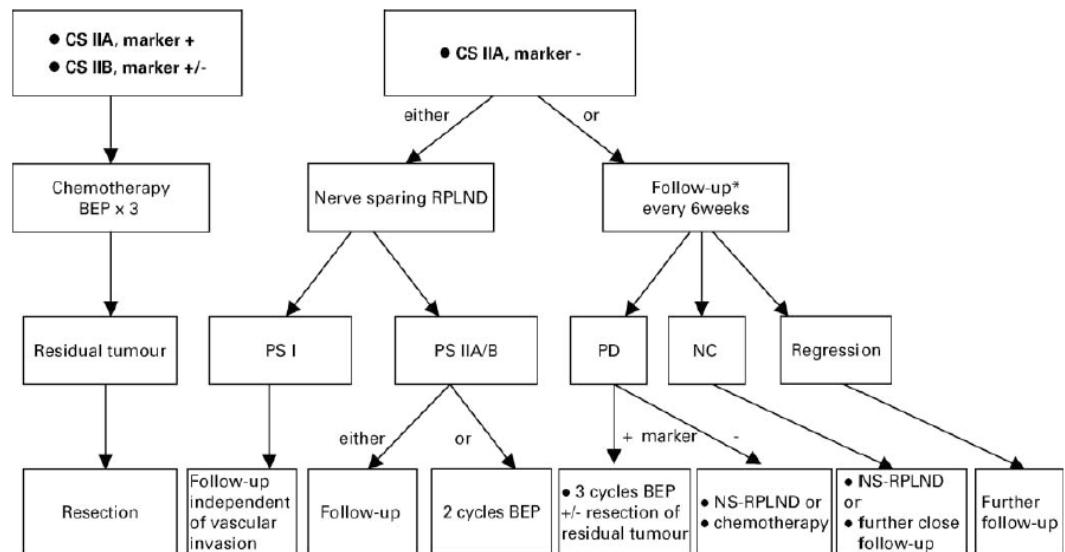
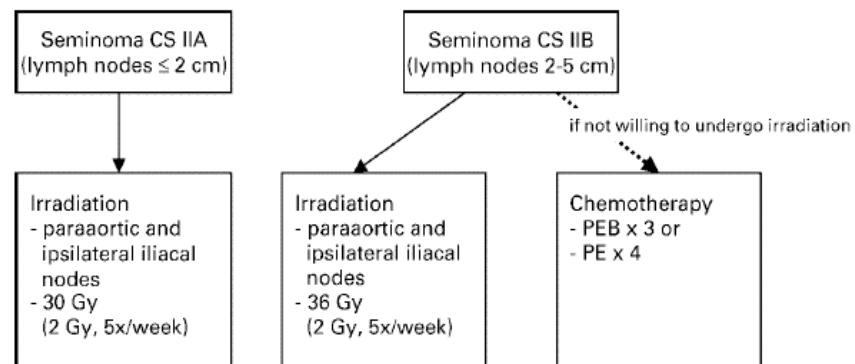


Treatment algorithm in Seminoma CS II A and B taken from EGCCCG guideline [58]



Treatment algorithm after orchiectomy according to individual risk factors in patients with Non Seminoma CSI, taken from EGCCCG guideline [58]

Treatment options in patients with Non Seminoma CS II A & B. Follow up if close surveillance is guaranteed with determination of tumour markers (every 6 weeks) and CT in short intervals, taken from EGCCCG guideline [58]



Treatment algorithm for advanced disease, taken from EGCCCG guideline [58]

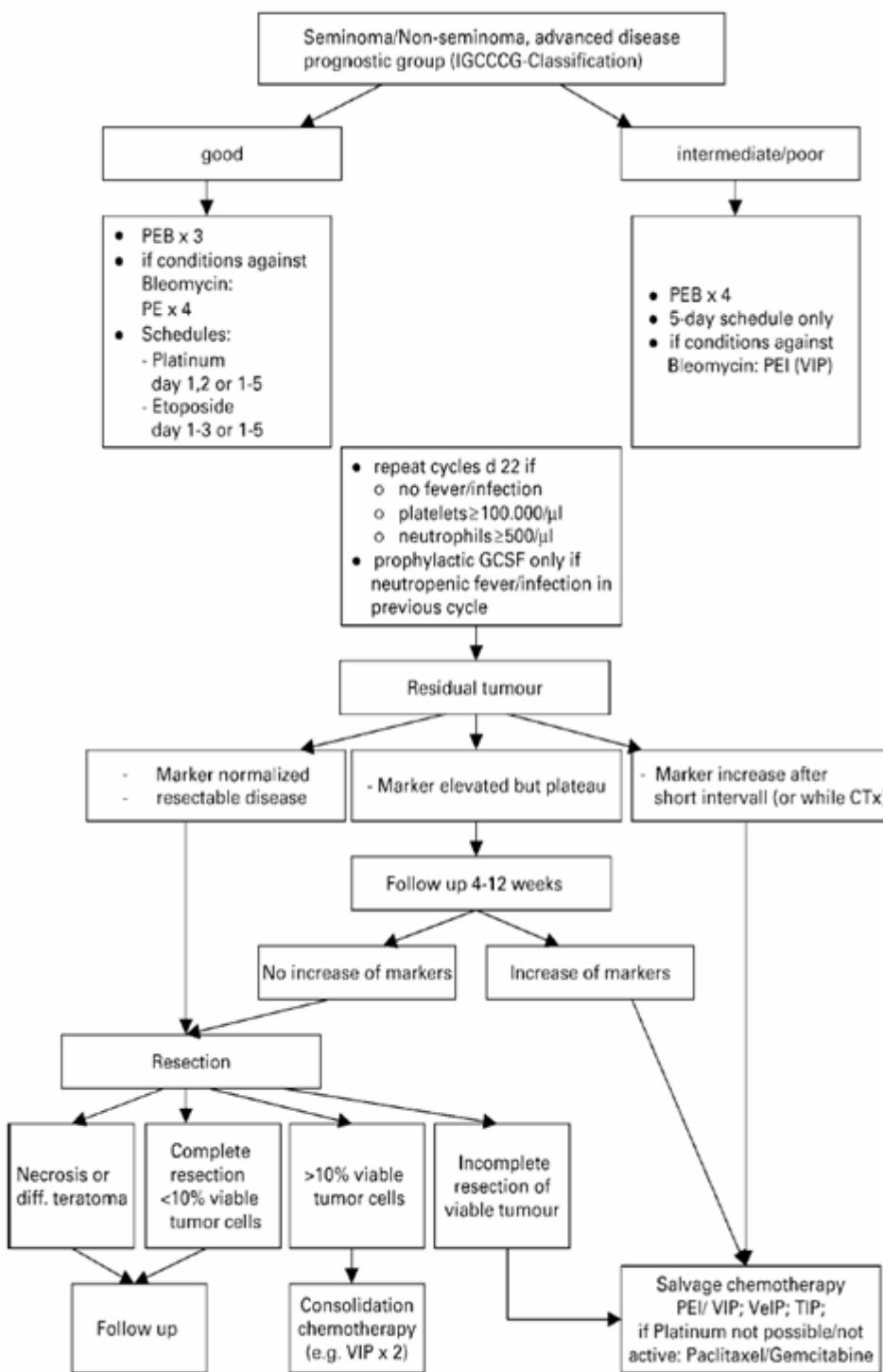


Figure 5. Treatment algorithm for advanced germ cell tumor.

APPENDIX 7: PROGNOSIS TABLE

(taken from EGCCCG guideline) [58]

**Table 3: Prognostic-based staging system for metastatic germ cell cancer
(International Germ Cell Cancer Collaborative Group)**

Good prognosis group	
<i>Non-seminoma</i>	
56% of cases	<i>All of the following criteria:</i>
5-year PFS 89%	<ul style="list-style-type: none"> • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/ml • β-hCG < 5,000 mIU/L (1,000 ng/ml) • LDH < 1.5 x ULN
5-year survival 92%	
<i>Seminoma</i>	
90% of cases	<i>All of the following criteria:</i>
5-year PFS 82%	<ul style="list-style-type: none"> • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
5-year survival 86%	
Intermediate prognosis group	
<i>Non-seminoma</i>	
28% of cases	<i>All of the following criteria:</i>
5 years PFS 75%	<ul style="list-style-type: none"> • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP > 1,000 and < 10,000 ng/ml or • β-hCG > 5000 and < 50,000 mIU/l
5-year survival 80%	<ul style="list-style-type: none"> or • LDH > 1.5 and < 10 x ULN
<i>Seminoma</i>	
10% of cases	<i>Any of the following criteria:</i>
5-year PFS 67%	<ul style="list-style-type: none"> • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
5-year survival 72%	
Poor prognosis group	
<i>Non-seminoma</i>	
16% of cases	<i>Any of the following criteria:</i>
5-year PFS 41%	<ul style="list-style-type: none"> • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/ml or • β-hCG > 50,000 mIU/L (10,000 ng/ml)
5-year survival 48%	<ul style="list-style-type: none"> or • LDH > 10 x ULN
<i>Seminoma</i>	
No patients classified as poor prognosis	

PFS = progression-free survival;

AFP = alpha-fetoprotein;

β -hCG = beta-human chorionic gonadotrophin;

LDH = lactate dehydrogenase

APPENDIX 8: TREATMENT PROTOCOL FOR ADVANCED DISEASE

(taken from EGCCCG guideline) [58]

Table 9. Chemotherapy protocols for treatment of advanced germ cell cancer

	Cisplatin, mg/m ² (30 min.-inf.)	Etoposide, mg/m ² (30–60 min.-inf.)	Ifosfamide*, mg/m ² (1 h-inf.)	Bleomycin, mg/m ² (IV bolus)	q day	No. of cycles/prognosis	
						Good	Intermediate/poor
BEP, PEB “5 days”	20 d 1–5	100 d 1–5	-	d 1, 8, 15	22	3	4
BEP, PEB “3 days”	50 d 1, 2	165 d 1, 2, 3	-	d 1, 8, 15	22	3	-
PE	20 d 1–5	100 d 1–5	-	-	22	4	-
PEI, VIP**	20 d 1–5	75 d 1–5	1200 d 1–5	-	22–29	-	4

*Mesna: 400 mg IV before the day 1 ifosfamide dose and then 1,200 mg/ day by continuous IV infusion on day 1 to 5 (120 hours).

**PEI/ VIP only if contraindication against Bleomycin.

BEP, cisplatin, etoposide and bleomycin; PEI, cisplatin, etoposide and ifosfamide; VIP, etoposide, ifosfamide and cisplatin.

APPENDIX 9: BELGIAN ONCOLOGY GUIDELINES WEBSITE

**Informatisation du guideline « cancer
colorectal »
Rapport final**

François Roucoux

Le 25 mars 2006

RAPPEL DE LA MISSION

L'objectif initialement fixé pour ce projet était le développement d'un outil de publication de guidelines, convivial et interactif, accessible sur le web et éventuellement utilisable comme système d'aide à la décision.

La publication de guidelines sous une forme interactive nécessite la traduction du texte du guideline dans un format informatique adapté. Idéalement, cette étape de traduction devrait pouvoir être réalisée par un expert du domaine (un médecin oncologue) et ne pas nécessiter de connaissances informatiques étendues.

C'est le langage de modélisation PROforma qui a été retenu pour le projet. Les critères principaux pris en compte dans ce choix sont décrits dans l'offre initiale. Succinctement, c'est l'existence d'un formalisme graphique, la disponibilité d'une implémentation concrète utilisée avec succès dans d'autres projets et la possibilité d'exploiter les guidelines modélisés comme outils d'aide à la décision qui a prévalu.

Les principales étapes du projet

La modélisation des guidelines dans le langage PROforma

La première étape du projet a consisté à modéliser les guidelines à l'aide du langage PROforma.

Le texte des guidelines a, tout d'abord, fait l'objet d'une lecture et d'une analyse sémantique fouillée. Les deux guidelines : cancer colique et cancer rectal ont chacun été analysés distinctement.

Cette analyse a permis de découper les guidelines en sous unités relativement indépendantes. Une description du langage PROforma est présentée dans l'offre initiale. Rappelons simplement que PROforma modélise un guideline sous la forme d'un « plan racine » composé d'une séquence de tâches et de « sous plans ». Le plan constitue donc l'unité de modularisation de ce langage.

Pour les deux guidelines, les « plans » suivants ont pu être dégagés :

- Situation d'urgence
- Procédure diagnostique
- Stadification clinique
- Première réunion multidisciplinaire
- Procédure chirurgicale
- Procédure histologique
- Classification finale
- Traitement des métastases résécables
- Traitement des métastases non résécables
- Suivi

Il existait une bonne corrélation entre ces « plans » de premier niveau et les items de la table des matières des deux guidelines.

Les sections du guidelines correspondant à chacun de ces plans ont, à nouveau, fait l'objet d'une analyse sémantique pour aboutir à la définition des sous tâches constitutives de chacun des plans :

Les collectes de données (enquiries) : qui correspondent généralement aux données nécessaires à la prise de certaines décisions (ex. : l'âge du patient, son taux de CEA, le résultat d'un examen complémentaire, ...). Le modèle réalisé tient compte du fait que certaines de ces données peuvent être inconnues.

Is a 3 generations extensive family history required ?

Are there 1 or 2 family members diagnosed with colon cancer ?

- No
- Unknown
- Yes

Has the patient a concomitant or previous ovarian or endometrium cancer ?

- No
- Unknown
- Yes

Figure 1 Une collecte de données

Les actions : essentiellement des recommandations prodiguées au médecin quant à la poursuite des étapes du guideline.

Colonoscopy and biopsy

Colonoscopy with biopsy is recommended for every patient with suspected colon cancer.

Pay attention to the good orientation of the specimen. It is a quality criteria for endoscopist and pathologist.

The biopsy must give answers to the following questions :

- Malignant or benign ?
- Is it a carcinoma within a polyp or an invasive cancer ?
- What is the differentiation grade of the tumour ?

Figure 2 Une action

Des décisions : elles correspondent à un ensemble d'options possibles. A chaque option est associée un ensemble d'arguments favorables ou défavorables. On associe à ces arguments des pondérations qualitatives ou quantitatives proportionnelles à la valeur de l'argument. Une règle de décision évalue les arguments de chacune des options et fournit au médecin un ordre de préférence quant au choix des options. La décision finale incombe toujours au médecin.

Is a 3 generations extensive family history required ?

- ★ This patient seems to have suspected hereditary conditions. A 3 generations extensive family history is required.
 - Because the patient is younger than 50.
 - Because 1 or 2 family members were diagnosed with colon cancer.
- This patient don't seems to have suspected hereditary conditions.
In this case, a 2 generations family history is sufficient.

Figure 3 Une décision : L'option recommandée est repérée par une étoile. La pondération des arguments est indiquée à l'aide de LEDs colorées.

Des sous plans : jusqu'à quatre niveaux hiérarchiques ont été modélisés dans les deux guidelinest.

Ce processus de modélisation itératif a aboutit à un modèle rigoureux et fouillé, mais relativement complexe, de chacun des guidelines.

La dernière étape du processus de modélisation a consisté à tester de manière intensive les modèles des deux guidelines pour s'assurer de leur validité.

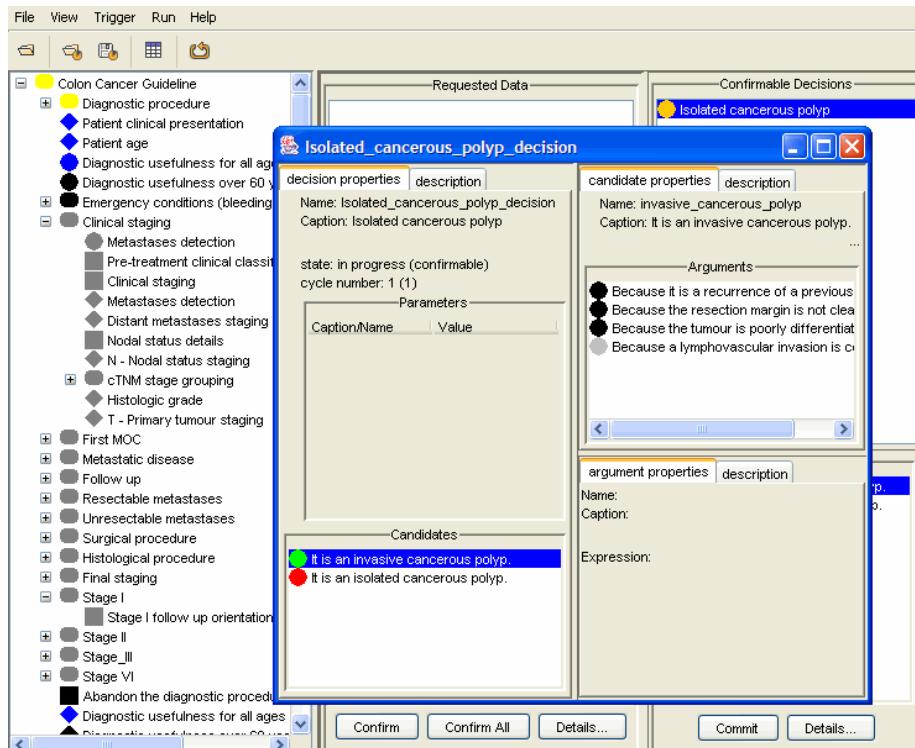


Figure 4 Procédure de test du modèle du guideline "cancer colique"

Le développement de la première version du portail

L'étape suivante a consisté à réaliser les développements informatiques nécessaires à l'implémentation des cas d'utilisation.

Schématiquement, le portail est constitué des éléments suivants :

Une interface d'utilisation qui permet aux utilisateurs d'interagir avec le portail et les guidelines qui y sont publiés.

D'un point de vue technique, cette interface est codée sous la forme de page JSP (Java Server Pages). Une couche d'internationalisation permet une spécialisation linguistique aisée de l'interface. La traduction, langue par langue, des textes de l'interface est aisément modifiable et extensible. L'interface a été réalisée en trois langues : anglais, français et néerlandais.



Figure 5 L'interface d'utilisation du portail (page d'accueil)

Une base de donnée qui sert au stockage :

- des données administratives relatives aux utilisateurs ;
- des guidelines publiés sur le portail ;
- des sessions d'utilisation de guidelines entamées par les utilisateurs.

D'un point de vue technique, la base de donnée, implémentée en Java, est orientée objet et non relationnelle. Cette caractéristique facilite l'importation des structures de données du système (logique administrative, interpréteur de guideline) directement dans la base et permet de simplifier les développements. En outre, la base de donnée est ainsi incluse directement dans le portail ce qui ne nécessite pas l'installation d'un SGBD (Système de Gestion de Base de Donnée) annexe.

Un interpréteur de guideline : ce composant est responsable de l'exécution du modèle PROforma des guidelines. C'est lui qui confère aux guidelines publiés sur le portail leur caractère dynamique et interactif. D'un point de vue technique, cet interpréteur, développé en Java, implémente strictement la spécification du langage PROforma dans sa version 1.3.38.

L'implémentation de la logique administrative du portail. Technique, il s'agit d'un ensemble de Servlets Java qui implémentent l'ensemble des fonctions administratives du portail. Ces fonctions sont décrites succinctement dans la suite de ce document et en détail dans le document intitulé : « Mise en ligne du guideline « cancer colorectal » Expression des besoins fonctionnels ».

Ces développements se sont étendus sur une durée d'un mois et demi.

La mise en ligne de la première version du portail

Le 11 février 2006, la première version du portail est mise en ligne pour les membres du conseil d'Oncologie.

Proposition d'un mode de présentation mixte des guidelines :

Une présentation interactive détaillée, basée sur PROforma et pouvant donc être utilisée comme système d'aide à la décision.

Une présentation simplifiée qui permet de naviguer rapidement dans un guideline.

Le 24 février 2006, la seconde version du portail est mise en ligne. Cette seconde version comporte une série d'améliorations, essentiellement visuelles, demandées par les membres du Conseil d'oncologie ainsi que la version des deux guidelines sous forme de cartes conceptuelles.

Les principales fonctionnalités du portail

La mise à disposition des fonctionnalités du portail s'articule autour de la notion de types d'utilisateur qui possèdent des droits spécifiques.

Trois types d'utilisateurs accèdent au portail :

- Les visiteurs ;
- Les consultants ;
- Les administrateurs.

Les visiteurs peuvent :

- choisir leur langue d'utilisation ;



Figure 6 Sélection linguistique

- effectuer une demande d'inscription ;
- consulter les versions textuelles des guidelines présents sur le portail sous forme de fichiers PDF et de cartes conceptuelles.

Les consultants peuvent :

- consulter la liste des guidelines disponibles sélectionner un de ceux-ci pour entamer une session d'utilisation interactive ;

Nº	Name	Description	Author	Version	
1	Rectum Cancer	Rectum Cancer Diagnosis and Treatment	NOG	14/02/2006	X
2	Colon Cancer	Colon Cancer Diagnosis and Treatment	NOG	14/02/2006	X

Figure 7 Sélection des guidelines disponibles

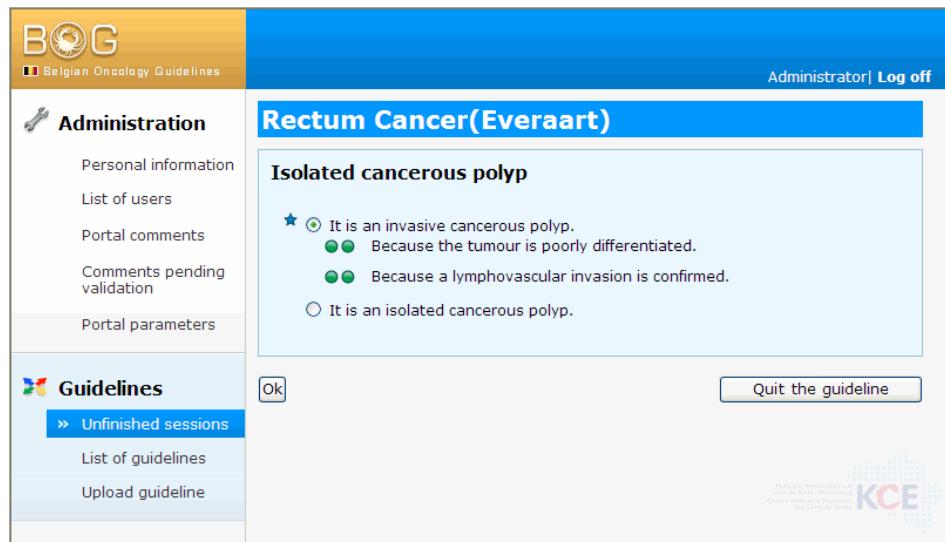


Figure 8 Consultation d'un guideline sous forme interactive

- poursuivre une session d'utilisation entamée lors d'un accès précédent au portail ;
- poster un commentaire en rapport avec un guideline particulier ou avec l'ensemble du portail ;
- modifier certaines caractéristiques de leur profil d'utilisateur.

Figure 9 Interface de modification du profil d'un utilisateur

Les administrateurs peuvent :

- ajouter un nouvel utilisateur au système ;
- promouvoir, rétrograder ou supprimer un utilisateur ;
- modifier certains paramètres de fonctionnement du portail ;

- publier, mettre à jour ou retirer un guideline ;
- valider les commentaires postés par d'autres utilisateurs.

Les auteurs de guidelines constituent un cas particulier d'utilisateurs. Ils accèdent au portail soit comme consultants, soit comme administrateurs. Ils disposent ainsi des droits respectifs de ces types d'utilisateurs. En outre, ils disposent du modeleur graphique qui leur permet de modifier ou de créer des guidelines. Ces guidelines doivent ensuite être transmis aux administrateurs du portail pour être publiés.

La mise à disposition de guidelines sous forme de cartes conceptuelles

La cartographie conceptuelle

La cartographie conceptuelle (concept mapping) est une technique de représentation graphique de la connaissance sous forme de cartes. Elle trouve son origine dans les années soixante suite aux travaux du Professeur Joseph D. Novak à la Cornell University. Cette technique a, depuis, été utilisée avec succès dans de nombreux domaines, dont l'enseignement et la dissémination des connaissances.

Les cartes conceptuelles sont simplement des réseaux constitués de nœuds et d'arcs. Les nœuds représentent des concepts et les arcs, les relations sémantiques qui existent entre ces concepts. Ces relations peuvent être non-, uni- ou bidirectionnelles. Les concepts ainsi que les relations peuvent également être catégorisés. Les relations, par exemple, peuvent être causales ou temporelles (deux types de relations couramment utilisées dans la représentation d'un guideline).

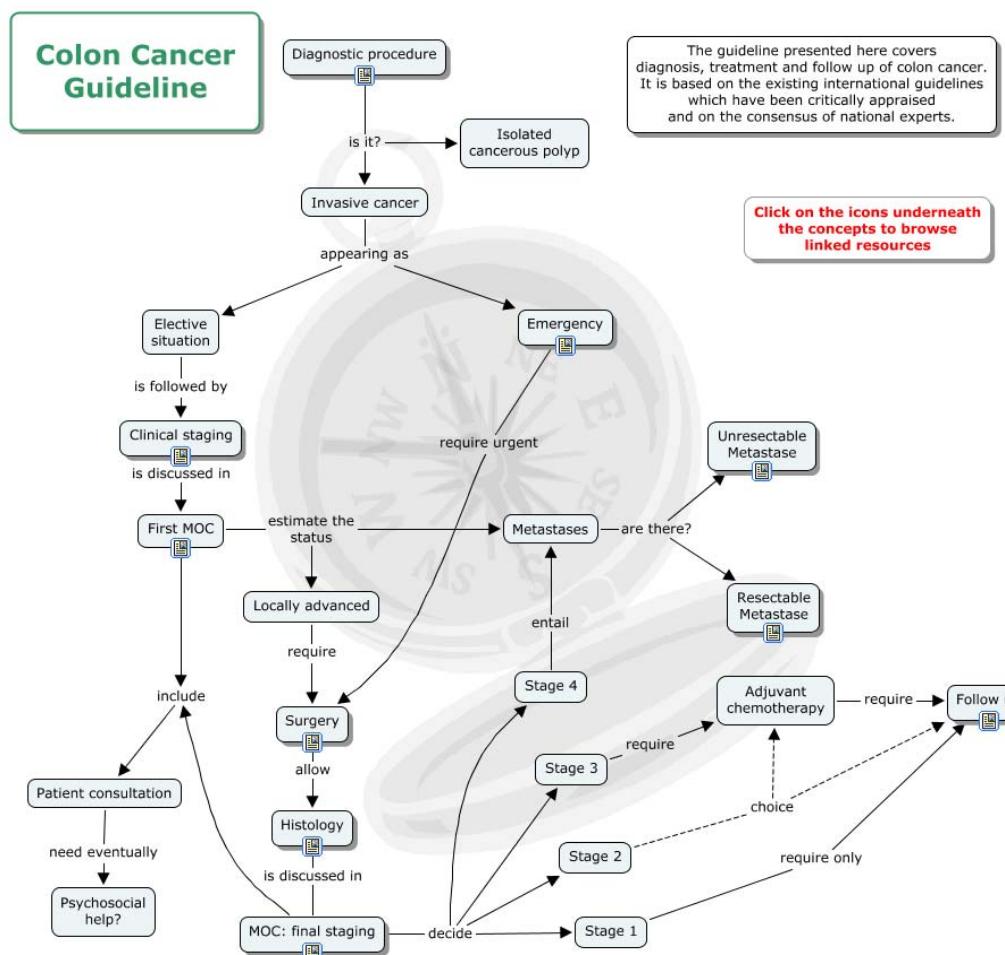


Figure 10 Représentation du guideline "cancer colique" sous forme de carte conceptuelle. Certains noeuds (repérés par une icône) permettent d'accéder à des ressources (textes, matériaux multimédia, autres cartes)

Les cartes conceptuelles sont particulièrement bien adaptées à la représentation de guidelines. Ceux-ci comportent d'ailleurs généralement une représentation graphique de leur déroulement ou algorithme.

Caractéristiques techniques

Tous les outils réalisés et mis à disposition dans le cadre de ce projet utilisent un environnement d'exécution Java. Ils peuvent donc être installé sur une large gamme de machines et d'OS (Windows 2000, XP, server 2003, Linux, Mac OS X, Solaris, ...) sans adaptations particulières.

Un serveur d'entrée de gamme relativement récent et doté de 512 MB de mémoire (! variation en fonction de l'OS utilisé) et d'un espace disque suffisant fera parfaitement l'affaire.

L'interopérabilité des développements effectués avec d'autres systèmes

Intégration ultérieure dans un système d'information hospitalier

Le terme « intégration » doit faire l'objet d'une définition plus précise. L'accès au système, hébergé par exemple sur un serveur du ministère, depuis n'importe quel hôpital ne pose pas plus de problèmes que celui de l'accès à un site protégé par identifiant et mot de passe. Par contre, si le système hébergé au ministère doit accéder à des données patients (résultats de biologie, d'examens complémentaires, ...), les choses se compliquent essentiellement à deux niveaux :

Du point de vue de la sécurité : des données sensibles doivent transiter sur l'Internet ce qui nécessite d'établir un consensus sur un protocole de sécurité commun à tous les hôpitaux.

Du point de vue du format de transmission : les données en provenance de tous ces hôpitaux doivent être intelligibles par le système. Or, à l'heure actuelle, et malgré l'existence d'initiatives telles que le protocole Kmehr-bis et la certification dont il fait l'objet, les systèmes d'information hospitaliers sont encore très peu normalisés ce qui impliquerait des développements spécifiques dans la majorité des hôpitaux désireux de fournir ces données.

La solution qui consiste à installer le système dans l'intranet de chaque hôpital permet de contourner ces deux difficultés mais en soulève une troisième quant aux mises-à-jour des guidelines et du système lui-même.

La plate-forme Be-Health pourrait apporter une solution élégante au problème en assurant l'accès sécurisé aux systèmes d'information hospitaliers. Le portail deviendrait un « client » de certains services offerts par Be-Health (identification, autorisation, validation des sources, ...).

A la fin de ce projet, il semble encore difficile de quantifier les développements nécessaires.

Intégration ultérieure d'un système d'aide à la décision

L'utilisation du langage de modélisation PROforma et d'un interpréteur pour ce langage comme composant du système lui confère les capacités d'un système d'aide à la décision. Je ne pense donc pas qu'il soit nécessaire d'envisager l'intégration d'un système d'aide à la décision supplémentaire.

Si une telle intégration semblait néanmoins souhaitable, le temps consacré à son développement dépendrait surtout des facteurs suivants :

La nature de cette intégration : s'agirait-il d'un simple lien vers ce système ou au contraire d'une intégration beaucoup plus poussée par exemple à l'aide de « web services » ?

Le système d'aide à la décision choisi : offre-t-il une interface de programmation adéquate ou un protocole de communication adapté ?

Il m'est difficile de quantifier ces développements sans avoir défini la nature de l'intégration et choisi le système cible.

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Wettelijk depot : D/2006/10.273/12

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase I). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel I. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkancerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico-legale aspecten van klinische praktijkrichtlijnen. D/2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D/2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D/2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D/2006/10.273/12.
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31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkancerscreening. D/2006/10.273/17.
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