RARE HEPATO-BILIARY CANCERS

PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

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PREFERRED MODEL OF CARE AND CRITERIA FOR REFERENCE CENTRES

A. Type of cancer

Hepatocellular, intrahepatic and proximal bile duct cholangiocellular cancer, gallbladder cancer, vascular tumours

B. Short description of the cancer

Hepatocellular cancer (HCC)

HCC ranks as the fifth most common cancer worldwide and the third most common cause of cancer mortality. Together with intrahepatic cholangiocellular cancer (IH-CCC) about 500 new cases are diagnosed every year in Belgium. Extrahepatic bile duct and gallbladder tumours are less frequent; their yearly incidence in Belgium is around 300.

The difficulty in relation to the treatment of these tumours mostly relies to the fact that the patient presents two diseases, the tumour and the very frequently present underlying liver disease.

Most primary liver tumours (up to 95%) are diagnosed in patients presenting an underlying liver disease mostly due to HCV and HBV infection, alcoholic (ALD) and non-alcoholic (non-alcoholic fatty liver disease NAFLD or, nonalcoholic steatohepatitis - NASH) liver disease.

At diagnosis, approximately 70% of patients are ineligible for curative surgery due to tumour extent and/or poor hepatic function. Surgery, either as partial or total hepatectomy, represents the only possible curative treatment. Different loco-regional therapies (LRT) such as percutaneous ethanol injection (PEI), radiofrequency (RF), trans-arterial (chemo-)embolization (TA(C)E) or radio-embolization (TARE) can stabilize or control the disease offering up to 50% three-years survival. LRT and/or interventional radiologic procedures aiming at raising the functional liver mass may enable patients to be brought back towards a resectable tumour status. In case of advanced and metastatic disease, target therapy using sorafenib (currently the only licensed drug) can prolong survival by some months.

Cholangiocellular cancer (CCC)

CCC can be present as an intrahepatic tumour mass or as an infiltrative process of the bile ducts. Tumours of the upper third of the bile duct are most frequent; when invading the primary biliary confluence they are termed Klatskin tumours. Chronic inflammation as seen in sclerosing cholangitis, lithiasis and fluke infestation is a frequent underlying cause of the disease.

The surgical treatment as well as prognosis of intrahepatic (IH-CCC) and proximal bile ducts tumours (EH-CCC) depends not only on the resectability but also on the residual liver function. Experience of the surgical team (R0 resection) supported by a specialized multidisciplinary hepato-biliary team is the main determinant in order to obtain good results, especially in case of the EH-CCC.

Indications for liver resection and transplantation have nowadays been very well established leading to five-years survival rates of up to 70% for HCC and 50% for CC. In some cases in which tumour extent and following surgical strategy could lead to an insufficient functional residual liver mass, interventional radiological procedures (such as portal and hepatic vein embolization, chemoembolization and biliary drainage) may allow to downgrade tumour burden and upgrade liver mass, allowing thereby to perform successful surgery. If surgery is contra-indicated, different LRTs may still offer good results usually up to 3 years survival. Experience of the surgical team is of paramount importance to select patient for curative resections.

Vascular tumours

Vascular tumours are diagnosed very rare. Haemangiosarcoma is an extremely aggressive tumour for which no effective treatment is nowadays available; hepatic epitheloid haemangioendothelioma (HEHE) in contrary can be cured by liver transplantation, even in case of limited extra-hepatic localisation 5-years survival rates of 80% can be obtained.

C. Model of care pathway suggested for adult patients with hepato-biliary cancer

Model of care pathway	Preferred model
1. Model 1: Reference Centres exclusively (from diagnosis to follow-up). Once there is a suspicion of a cancer or a cancer has been diagnosed, the patient should be referred to a Reference Centre. A network with other Reference centres or with specific experts working in other centres is encouraged.	
2. Model 2: Shared care between Reference Centres (RC) and Peripheral Centres (PC). Part of the care pathway is performed in the Reference Centre and for another part of the care pathway, the patient is referred (back) to the peripheral hospital	**X**

D. Phases of the clinical pathway for which Reference Centres are required

Phase of the Clinical Pathway	Reference Centre – RC	Peripheral Centre – PC
COM/MOC	All newly diagnosed patients have to be discussed at COM/MOC consisting of surgeon, radiologist, pathologist, (interventional) endoscopist, interventional radiologist, radiotherapist, nuclear medicine physician and digestive oncologist, all experienced in the field of HB oncology.	All newly diagnosed patients have to be discussed at COM/MOC consisting of surgeon, hepatogastroenterologist, radiologist, pathologist, (interventional) endoscopist and digestive oncologist and, if available, radiotherapist and nuclear medicine physician, all experienced in the field of HB oncology.
Diagnostic confirmation and staging	Review of diagnosis and staging quality of PC at a second opinion (tele-)COM/MOC.	The PC COM/MOC must be linked to the RC COM/MOC in order to confirm diagnosis and staging and to decide about the therapeutic strategy as well as modality.
Comprehensive diagnosis	State of the art diagnostic performance of imaging and pathology updated to the newest developments and driven by a dedicated medical and surgical HB team.	
Therapeutic modalities	The complete spectrum of all therapeutic modalities to be considered following interaction between all experienced caregivers in order to optimize patient care.	The spectrum of therapeutic modalities to be discussed with the RC in order to optimize patient care and to choose those treatments that can be done at the PC.
	Decision on surgical strategies including (complex) hepato-biliary surgery or liver transplantation.	Non complex hepatobiliary surgery (segmentectomy, atypical and wedge resections; laparoscopic radiofrequency)
	Loco-regional or systemic therapy Interventional endoscopy and/or radiology	Loco-regional or systemic therapy Interventional endoscopy and/or radiology on the condition that necessary expertise is available
Follow-up (FU)	Routine oncologic and hepatologic FU	Routine oncologic and hepatologic FU
	Follow-up related to downstaging program using (combination of) locoregional therapies in view of eventual transplantation or increasing resectability rate using interventional radiology	The spectrum of locoregional therapies to be discussed with the RC in order to optimize patient care and to choose those treatments that can be done at the PC.

Multidisciplinary Oncological Consult (COM/MOC): Reference Centre or Peripheral centre with a program in oncology

All newly diagnosed patients with HB cancer must be discussed at COM/MOC. The quality of diagnosis and tumour staging done at the PC must be reviewed by the RC [second opinion (tele-)MOC]. As most patients will present with an underlying hepato-biliary disease, interactivity between all involved caregivers experienced in HB oncology and hepatology is necessary in order to choose within the large spectrum of modalities not only the best therapy but also the one best adapted to the frequently present underlying liver disease. This is especially important when decisions about loco-regional or systemic neo-adjuvant and/or adjuvant therapy and/or complex surgical strategies, including liver transplantation, have to be taken. Indeed patients presenting with a similar tumour burden may have completely different treatment options depending on the underlying liver disease. Guaranteeing a continuity of the therapeutic 'strategy' is of paramount importance in these pathologies. The dedication of the medical and surgical HB teams will continuously trigger the experience of the departments of imaging and pathology, especially when implementing the more and more frequently applied neo-adjuvant and adjuvant treatments.

Diagnostic confirmation: Reference Centre

- Complexity and new approaches: Expert treatment of HB tumours more and more relies on state of the art imaging techniques (3 phase contrast CT or MRI; PET-scan; scintigraphy), refined pathology and complex hepato-biliary surgery. These 'moving' fields are of much importance for accurate tumour staging and surgical R0 procedures. In case of combined radiological and endoscopic diagnostic and therapeutic interventions, integration of expertise is needed.
- Facilities and equipment required: State of the art units of interventional radiology, endoscopy and intensive care with experience in treatment of liver failure.

Comprehensive diagnosis and staging: Reference Centre or peripheral pathology lab

Diagnosis of HB malignancies can be made in all centres if the pathologist has in his/her laboratory the necessary immune-histochemical (IHC) stains. In case of doubt or of a missing IHC test, the material can be sent for second opinion to a reference pathologist. In addition, in HB malignancies, biopsies will most often be done because imaging is not conclusive. These cases are the difficult ones and need to be sent directly to a reference centre. Review of PC diagnosis by 'tele-pathology' is eventually to be considered.

Mixed HCC-CCC, differential diagnosis between well-differentiated HCC and (atypical) adenoma in 'normal' livers, or with dysplastic nodules in the cirrhotic liver, differential diagnosis in vascular tumours have to be seen by a pathologist from RC.

After resection, appropriate handling of the surgical specimen can be done in all pathology laboratories, providing that they follow the guidelines from the literature and use the required IHC tests. Again, in case of doubt or missing IHC tests, referral to centre with special experience is advised. The pathology report has to indicate all the necessary information needed for appropriate patient care and for this purpose, the use of standardized report forms is recommended.

Tumour gene profiling and additional particular IHC tests will become more and more necessary to fine tune not only in diagnosis but also to assess prognosis and tailor future systemic treatments. This will be more available in RC with the support of the other members of the HB group. There is mostly no need for RC pathology to confirm diagnoses (see AASLD guidelines - American Association for the Study of Liver Diseases - and EASL guidelines - European Association for the Study of the Liver).

Therapeutic modalities: Collaboration between a peripheral centre with a program in oncology and a Reference Centre

The evaluation of both tumour (size, number, biology, staging, grading) and underlying liver function is necessary to offer state of the art treatment in HB oncology. Different experts (hepatologist, gastro-enterologist spending at least half of their professional activity in management of liver diseases, oncologist, radiologist, surgeon with expertise in extended liver surgical procedures, interventional radiologist, intensive care physician, anaesthesiologist, interventional endoscopist, transplantation surgeon/physician) are necessary to support the treatment choice.

Complex endoscopic and radiologic procedures, liver parenchyma sparing surgery, especially in cirrhotic patients, complex liver surgery for biliary tract tumours and liver transplantation must be centralised in RC.

Non complex hepato-biliary surgery can be performed in PC by surgeons trained in HPB surgery and in close interaction with the RC (consultant).

New protocols or clinical trials can be set up in collaboration with PC.

To streamline the model 2 of collaboration between RC and PC, uniform and standardized referral forms are necessary.

- Expertise required to perform the treatment
  - Endoscopy, radiology, hepato-biliary surgery and oncology;
  - Surgeons with experience in complex hepatobiliary surgery and liver transplantation when required;
  - Loco-regional treatment (intra-arterial chemotherapy or radio-nucleid treatment): the team needs experience on how to avoid and to treat liver failure as well as to recognize and treat infectious complications (sepsis and abscess formation) properly;
  - Systemic treatment: expertise necessary in order to handle side effects and to maintain proper dosing of drugs in liver patients;
  - Proper imaging interpretation necessary using standardized (m-RECIST) criteria or comparable methods to evaluate treatment response.

Follow-up: Collaboration between a Peripheral Centre with a program in oncology and a Reference Centre

Follow-up can be done in PC using a standardized, continuously re-evaluated, pathway care (EBM guidelines to be followed). State of the art imaging has to be performed following a well-defined scheme related to definitive (pathologic) tumour staging. This can only be done in PC if adequate infrastructure is available as well as expertise in interventional endoscopy and radiology, surgery and oncology.

The paramedical expertise required consists of dedicated nursing team, oncologic nurse specialist, nutritionist team, data nurses and data manager.

The evolution must be re-discussed at regular times and after each adverse event or major change in patient condition with RC during COM/MOC (e.g. by tele-MOC).

Every case of local or extra-hepatic tumour recurrence after interventional radiology as well as after resection surgery (especially in view of ‘rescue’ transplantation) and transplantation (especially in view of emerging adjuvant target therapies) is to be re-discussed at RC COM/MOC.

Follow-up of liver transplantation can be done in collaboration between RC and PC.

Follow-up of clinical trials should be concentrated in RC.

E. General and specific criteria for Reference Centres

Human Resources and dedicated team

Different studies in USA, and UK (high versus low volume), Germany (MM or 'mindest-mengen'), France and The Netherlands ('normen') showed that concentration of patients in HB oncology and transplantation favoured outcome. This is surely true for liver resection and transplantation but also seems to be of value for loco-regional (TACE, PEI, RF…) and even systemic treatments (e.g. sorafenib).

In a RC, two (or more) experts in the field of HB oncology have to be identified (cfr. Mayo model). One medical doctor should be the reference person in his/her field of expertise. S/he is responsible for all HB issues related to this expertise including scientific and educational activities, quality control and continuity of care. Under his/her guidance, the guidelines in relation to HB oncology should be updated to the most recent (EBM) knowledge and progress reports.

The RC must have COM/MOC consisting of specialists in all related fields of HB oncology. The reference medical doctor per speciality also represents his speciality at the second opinion COM/MOC. The set-up of an audio-visual infrastructure in order to allow not only a 'tele-MOC' but also to set up a reference network is desirable.

MOC meetings are to be held weekly. Morbidity-mortality MOC conferences have to be organized every six months (HB-MoMo-MOC), involving referring specialists from peripheral centres.

The team also consists of:

- nutritional team (Total Enteral Nutrition team);
- physiotherapy team;
- oncologic psychologist;
- data nurses and manager;
- specialized nursing team;
- oncologic nurse specialist.

HB oncologic nurse specialist is necessary in order to interconnect the medico-surgical teams and the paramedical teams and the patient and his family.

Required facilities and equipment

The RC has to be on one single hospital site. Up-to-date interventional endoscopic and radiological facilities and intensive care unit with experience in treatment of liver failure are required.

Following specialized units must be present:

- dedicated and advanced state of art diagnostic using standardized reporting forms;
- state of the art pathology department using standardized reporting forms (see PROCARE project);
- dedicated and advanced state of the art interventional radiology;
- dedicated interventional endoscopy unit;
- nuclear medicine;
- hepato-(pancreato) biliary surgical ward. Complex surgical procedures, including extended liver surgery to be performed in one single facility;
- liver transplantation unit or structured collaboration with centre performing liver transplantation;
- intensive care with experience in treatment of liver failure or collaboration with ICU experienced in liver disease or liver failure;
- anaesthesiology with experience in liver disease management;
- hepatology or hepato-gastro-enterology (unit);
- radiotherapy;
- pain clinic;
- HB oncology and gastro-intestinal outpatient clinic;
- access to rehabilitation program;
- infrastructure to conduct/participate in high quality clinical trials;
- set up of specialized database.

A 24/7 service must be available for all involved caregivers.

Patient centred care

An effective and time limited care pathway is very important in HB oncology. Factors related to tumour evolution, time and liver insufficiency indeed can progress very rapidly making any curative treatment impossible.

The optimal time-line is proposed as follows:

- Waiting time for first outpatient clinic visit is preferably one week;
- Time-span necessary for diagnosis and staging is preferably three weeks;
- Time-span to 1st COM/MOC and 2nd COM/MOC (RC) is maximally four weeks;

- Time-span between first visit and start of treatment is maximally six weeks;
- Deviation of proposed time-line is possible in particular cases; documented justification is necessary.

In order to respect such time-line, collaboration with other expert centres should be made possible.
After the MOC discussion, the general practitioner has to be informed of the therapeutic plan. The nurse specialist plays an important role in the transmission of information about diagnostic and therapeutic timeline and plan. Information flyers for patient and families and support service for patient and families are to be developed.

Minimal volume of patients

In Belgium, during the period 2004-2010, a yearly average of 520 new cases of epithelial tumours of liver and intrahepatic bile tract was recorded by the Belgian Cancer Registry.

A RC should treat 50 and a PC should treat 12 (one monthly) new (and unique) patients yearly.

In this context, surgical expertise is very important. Following literature data, the number of patients necessary to a centre to be recognized as a RC is however very variable. The number of 24 new patients has been advanced to distinguish high volume from low volume surgical centres (see references in addendum).

It is proposed that during a period of three successive years, 12 liver surgeries will have to be performed yearly (one monthly) in order to keep sufficient expertise.

Surgical treatment of the less frequent biliary tract cancers should be concentrated in some RC having a particular experience with this pathology.

Volume must be linked to quality and outcome after defined periods of 3 years in order to remain recognized as RC.

Quality Assurance

- All new patients have to be included in the RC and PC HB-Onco registries;
- Collaboration with existing Belgian Cancer Registry;
- The COM/MOC representatives have to adapt guidelines to most recent knowledge in the field (see for example EASL and AASLD guidelines);
- An annual detailed report including activity, tumour types, diagnostic and therapeutic guidelines, 3 months mortality and long-term (one and five-years) outcome is mandatory. Survival rates should be specified for all different (loco-regional and systemic) treatments as well as one and five-year survival after liver transplantation and mortality on liver transplantation waiting list;
- Use of and adherence to standardized imaging and pathology reports;
- Two-yearly Mortality-Morbidity HB oncology MOC meetings;
- Evaluation of the number of second opinions given by RC COM/MOC.

Research and other scientific activities

- Involvement in clinical studies (RCTs, cohort studies, translational studies);
- Publications in peer-reviewed national and international journals;
- Presentations at local, national and international conferences;
- Research projects and/ or grants;
- Mandatory link with a tumour bank;
- Development of clinical practice guidelines for diagnosis and care;
- Standard operating procedures should be available to all members of the involved teams and caregivers.

Educational activities: Teaching and dissemination

- Guaranteeing continuity of expertise in the RC by training of young staff members in expert high-volume centres;
- Regular scientific meetings for all members of the team highlighting progresses, new diagnostic and therapeutic modalities in general or in particular fields of the domain (role of coordinator COM/MOC);
- Regular meetings related to HB oncology for paramedical teams;
- Participation to postgraduate courses;
- Information and involvement of patient groups

Addendum. Documents consulted in relation to volume in HB surgery

1. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. Ann Surg. 2005;242(4):540-4; discussion 544-547.
2. Tol JA, van Gulik TM, Busch OR, Gouma DJ.Centralization of highly complex low-volume procedures in upper gastrointestinal surgery. A summary of systematic reviews and meta-analyses. Dig Surg. 2012;29(5):374-383
3. SONCOS Multidisciplinaire Normen Oncologische Zorg In Nederland. Naar een nog betere kwaliteit van behandeling van patiënten met kanker - 2013
4. NHS Standard Contract Hepatobiliary and Pancreas version 2012/2013 and AUGIS (Association Of Upper Gastrointestinal Surgeons Of Great Britain And Ireland) Guidance on minimum surgeon volumes; http://www.augis.org/pdf/reports/AUGIS_recommendations_on_Minimum_Volumes.pdf 2010