

New indications for radiotherapy: primary liver cancer and secondary liver oligometastases

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Surgery is considered to be the standard treatment for intrahepatic malignancies, primary cancers and metastatic lesions. However, a great many patients are not eligible for surgical intervention. Modern stereotactic radiotherapy has the potential to be an effective alternative treatment modality with low toxicity for patients with primary hepatocellular carcinoma and liver oligometastases. In this paper we intend to review the current status and published experiences in the field of liver irradiation.

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Introduction

Hepatocellular carcinoma (HCC) is the third most deadly neoplasm in the world. It is considered a rare primary malignancy in North America and Europe, in contrast to Asia and Africa.¹ Statistics of the World Health Organization (WHO) report over 600,000 HCC-related deaths per year worldwide. In Belgium the annual incidence is low. Of the whole population, 484 new cases were registered by the National Cancer Registry for 2006, but this number seems to be increasing continuously. The most common aetiology of HCC is chronic hepatic cirrhosis related to alcohol consumption, exposure to aflatoxin, metabolic or autoimmune diseases and hepatitis B or C viral infection. Theoretically, secondary liver metastases can occur with any invasive neoplasm, but the most frequently occurring primary tumours are colorectal, breast, stomach, pancreas and lung tumours.

The preferred treatment for HCC is surgery but the prognosis of the disease is poor, as at most 20% of

the patients is eligible for surgical resection or liver transplantation. The 5-year survival after total excision or transplantation is 12-55%.² Surgical removal, if feasible, is considered standard treatment for liver metastases. This approach yields interesting results in selected patients, but the indication for surgery is limited by the number, the localisation and the dimension of the lesions, the actual state of the primary tumour and the severity of the underlying hepatic disease.

Thus, there is room for non-surgical treatment modalities in the management of both primary and secondary liver malignancies. Modern, high precision radiotherapy techniques, able to administer a highly conformal radiation dose in a few fractions, have the potential to be as ablative as a surgical resection.³ After the recent launch of a Cyberknife® system, enabling stereotactic irradiation with unrivalled accuracy, the Department of Radiation Oncology of Liège University Hospital nowadays broadens the field of potential indications for

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radiotherapy to encompass primary and secondary liver tumours.

Management of the disease

In the management of HCC one of the most important factors for therapeutic decision making is the severity of the underlying hepatic disease, and hence the remaining functional capacity of the liver. To assess the prognosis of chronic liver disease the Child-Pugh classification system is used widely. Five clinical parameters are scored in this system: serum bilirubin, serum albumin, INR, severity of ascites and encephalopathy. For patients in Child-Pugh class A and for some patients in class B, surgical resection could be the preferred treatment if technically and clinically feasible. For unresectable tumours, and in Child-Pugh class C, the possibility of including the patient in an orthotopic liver transplantation programme has to be evaluated.

A detailed treatment decision tree has been published by the Barcelona Clinic.⁴

For secondary liver metastases, surgeons consider resection as the preferred treatment whenever possible. Nowadays, a large number of non-surgical treatment modalities is available. The indications for these techniques differ and the accessibility can vary from one institution to another. We intend to review non-surgical treatment options and focus especially on highly conformal ablative radiotherapy.

Chemotherapy has a limited role to play in the treatment of HCC, but in contrast, it is of major importance to the treatment of secondary malignancies in the liver. However, more recently a new drug for the treatment of primary hepatocellular carcinoma has been put forward: sorafenib (Raf kinase inhibitor, vascular endothelial growth factor receptor (VEGFR) inhibitor and platelet-derived growth factor (PDGFR) inhibitor).

Non-surgical local treatment modalities

A non-surgical treatment approach for HCC is considered in case of technical unresectability, as neoadjuvant treatment before resection, or as therapeutic strategy before orthotopic liver transplantation. In the latter case the treatment is often called bridging therapy with the intention of decreasing or stabilising the disease until a donor is found and the

planned surgical intervention can be realised.

Percutaneous ethanol injection (PEI) is one of the non-surgical approaches based on the injection of 95% alcohol into the tumour. Tumour size should not exceed 2 cm and the injections frequently have to be repeated. An alternative approach is radiofrequency ablation (RFA). This is a heat-based ablation, obtained through placement of the needle within the tumour, which should not exceed 3-5 cm, and which should not be close to a large vessel in order to ensure the ablative temperature is obtained.

Other alternatives are transarterial embolisation (TAE) with bland particles, and transarterial chemoembolisation (TACE). For the latter technique a variety of choices in embolising material (polyvinyl alcohol, gelatine sponge) and chemotherapy agents (mitomycin, doxorubicin, cisplatin) is currently available. In theory, there is no limitation for this technique in terms of tumour size.

Other local treatment approaches to hepatic lesions include cryoablation, percutaneous laser ablation, microwave ablation and radioembolisation (radioactive isotopes attached to embolising material: TheraSphere, SIR-Sphere). Very often, local treatment modalities are combined sequentially or synchronously.

Radiotherapy as local treatment

Liver neoplasms, whether primary or secondary, are not considered to be classical indications for radiotherapy. This is mainly due to the tolerance of normal liver tissue to ionizing irradiation. However, as early as 1990, the University of Michigan reported their experience in irradiation of liver tumours with conformal 3D RT.⁵ In a phase II study, Mornex et al. in Lyon, France achieved 78% complete response with a dose of 66 Gy /2 Gy fractions in 27 patients with small (<5 cm) primary HCC.⁶

For conventional 3D-based radiotherapy regimens, low doses per fraction (1.5-1.8 Gy) are used, eventually resulting in 2 fractions a day. Using such hyperfractionated schedules, dose-escalation studies have been performed, illustrating a clear dose-response relationship in case of HCC and metastatic liver lesions.⁷⁻¹⁰ Optimal imaging for tumour delineation, high dose conformality and hence low doses on surrounding healthy tissue, and taking target motion linked to respiration into account, yields

Table 1. Studies on stereotactic radiotherapy of hepatocellular carcinoma.

Author (reference)	Number of patients	Dose (Gy) (fraction x dose per fraction)	Overall survival (months) y = years	Local control	Toxicity ≥ grade (G) 3
Mendez et al 2006. ²³ Phase I/II	25*	3 x 10-12.5 5 x 5	Actuarial 1y/2y: 75%/45% for HCC 85%/62% for metastases	1y 94% 2y 82%	Acute 2 G3 enzyme ↑ 1 G3 asthenia 1 G5 death Late 1 G3 portal hypertension syndrome
Tse et al 2008. ¹⁸ Phase I	41#	6 x 4-9	Median 13.4 m 1 y 51%	1y 65%	Acute 10 G3 enzyme ↑ 1 G3 thrombopenia Late 2 G1 (1 death)
Choi et al 2008. ²⁰	31	3 x 10-13	Median 11.5 m 1 y 81.4 %	Overall response rate 71.9%	Acute 1 G3 enzyme ↑ 5 progression of Child-Pugh class
Son et al 2010. ²²	47	3 x 10-13	-	-	Acute 12 G2 or higher hepatic toxicity 4 progression of Child-Pugh class

*=17 liver oligometastatic patients, 8 HCC patients, #=10 intrahepatic cholangiocarcinoma.

the opportunity for hypofractionation. For this type of treatment schedule a limited number of fractions (typically 2-5), possibly a single fraction, are applied resulting in a much higher biological effect. The latter can be compared to surgical removal and hence is called ablative radiotherapy. These techniques are reported as stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery.

In these techniques a high number of usually non-coplanar photon radiation beams are used making high conformality and steep dose gradient around the tumour possible, resulting in a decrease of the dose on surrounding normal tissue.

There are 2 ways to administer such highly conformal treatments. Firstly, the conventional linear accelerator based SBRT with stereotactic body-frame to assure accurate immobilisation. This approach is not new; the Karolinska Institute in Sweden published the first experience with abdominal stereotactic treatments in 1994.¹¹ Image guidance with respiratory gating in accelerator based SBRT is critical, as the liver and therefore the target lesion can move 2.5 cm in superior-inferior direction due to respiration.¹²⁻¹⁵ This technique is usually applied under abdominal compression to decrease the respiratory related displacement of the diaphragm, and hence the liver. Motion due to breathing can also be compensated by gating or by active breathholding

techniques. For the latter techniques the beam is continuously switched on and off, obviously prolonging the overall treatment time. The second approach involves a dedicated system such as the robotic frameless Cyberknife® System.

The 6 MV accelerator, mounted on a robotic arm, has 6 degrees of freedom in movement. It has the capacity of using hundreds of beam positions on a half-sphere surface around the patient. Implantation of small gold fiducials in the immediate surroundings of the target, especially in liver tumours, is a prerequisite for the X-ray near real-time tracking of the tumour. Using infrared (IR) light emitting diodes on the surface of the thorax and an IR detector, the system is able to follow the respiratory related displacement of the target, and maintain continuous beam administration. This system can easily administer non-isocentric treatments in case of irregular tumour shapes.

Radiotherapy with heavy charged particles is another encouraging treatment option but cannot be considered routinely as yet. The team of Chiba reported 87% 5-year local control rate in a study of 162 HCC patients treated with proton RT (median dose of 72 Gy/4.5 Gy fractions).¹⁶ Proton therapy is characterized by precise energy deposition at a depth defined by the energy of the entrance beam (Bragg peak), while minimizing entrance dose and eliminating dose behind the

Table 2. Studies on stereotactic radiotherapy of liver metastases.

Author (reference)	Number of patients	Dose (Gy) (fraction x dose per fraction)	Overall survival m=months y = years	Local control	Toxicity ≥ grade 3
Herfath et al 2001. ²¹	37 [§]	1 x 14 – 1 x 26		18 m 81%	No G3 toxicity
Katz et al 2007. ²⁷	69	Total of 30-55 Gy in 2-6 fr	Median 14.5 m	10 m 76 % 20 m 57 %	No G3 toxicity
Rusthoven et al 2009. ³ Phase I/II	47	3 x 12 – 3 x 20	Median 20.5 m 2 y 30%	1 y 95% 2 y 92%	Late 1 soft tissue breakdown
Lee et al 2009. ²⁴ Phase I	68	6 x 7 (median) 6 x 4,6-10	17.6 m	1 y 71 %	Acute 2 G3 enzyme ↑ 3 G3 thrombopenia 4 progression of Child-Pugh class 2 G3 gastritis/oesophagitis
Van der Pool et al 2010. ²⁵ Phase I-II	20	3 x 12,5-15	74%	83%	2 G3 enzyme↑ 1 G3 physical weakness

[§] 33 metastases, 4 primary HCC

Bragg peak. In this context, dealing with target motion becomes an essential and yet unresolved issue. Proton beam radiotherapy is not yet available in Belgium.

Indications and limitations of stereotactic liver irradiation

Stereotactic high precision radiotherapy in primary HCC can be the preferred treatment as bridging therapy to stabilize or decrease the lesion in patients waiting for liver transplantation. Some patients will be waiting as long as a year for surgery. It can even be considered as the principal local treatment option in cases where neither resection nor transplantation are feasible.

In the treatment of hepatic oligometastases (1-3), the indication is even more well-founded according to the results of a recent phase I/II trial, reporting that SBRT can be as effective as surgical removal.³ Of course, for both primary and secondary liver lesions, radiotherapy can be combined with other non-surgical treatment options as well.

The size and the number of the lesions can be a contraindication for the RT treatment. In most studies, patients are eligible, provided they present 1-3 lesions, with a maximum diameter of 5-6 cm. Care should be taken, when considering SBRT, that a certain volume of healthy liver tissue is spared. When

performing dosimetric evaluation of SBRT prior to treatment, normal tissue complication probability models (NTCP) can be used to predict the risk for surrounding normal tissue. In case of liver disease, gold markers should be implanted in order to allow tracking and to limit margins around the target volume. Because of the invasive nature of fiducial placement coagulation dysfunction represents a contraindication (Child-Pugh C). Portal vein thrombosis however, is not a contraindication for SBRT, in contrast to other treatment options, such as PEI and TACE. Even centrally located tumours can be treated with SBRT although the vicinity of stomach and bowel close to the high dose region can be a technical problem.

Reported experiences in liver SBRT

A growing number of publications reveal the potential role of stereotactic RT in the treatment of primary liver tumours and liver metastases.^{9,17-28} Survival and local control rates and the dose-fractionation schedules are shown in *Table 1* (page 10) and 2. Total dose and dose per fraction, and hence total number of fractions are different but generally, a hypofractionated schedule is used. A number of studies are designed to investigate dose escalation. In liver metastasis a stereotactic treatment of 60 Gy

Key messages for clinical practice

1. High precision modern stereotactic radiotherapy is a safe, minimally invasive treatment option for liver lesions.
2. High local control rates can be achieved.
3. Optimal total dose and number of fractions should be further investigated in clinical trials.

in 3 fractions can be administered without dose-limiting toxicity.^{3,26} If a single-fraction treatment is used, the dose administered can be as high as 26 Gy. The 1-year and 2-years local control (LC) rates are very promising: 95% and 92% respectively for liver metastases and 94% and 82% respectively for mixed study population of HCC and metastases.^{3,23} In a study population with only primary HCC, 65% 1-year LC has been achieved.¹⁸ When receiving the pathological report after orthotopic liver transplantation due to oligometastases, a complete pathological response as high as 42% has been reported.²⁸

Toxicity

Most common acute toxicities of SBRT are chills, pain, fever, loss of appetite, nausea-vomiting, fatigue, gastritis, oesophagitis, thrombocytopenia and deterioration in liver functions. Radiation-Induced Liver Disease (RILD) consisting of hepatomegaly, ascites and elevated liver enzymes, usually appears 30-60 days after RT. Late toxicities are gastrointestinal ulcer, non-traumatic rib fracture and definitive deterioration in liver functions causing progression in Child-Pugh class. Toxicity data are presented in *Table 1* (page 10) and 2.

Even now, some data are available on dose-volume constraints especially for hepatic function. Dawson et al. suggest a TD 5/5 (tolerance dose resulting in a normal tissue complication probability of 5% within 5 years after RT) of 31 Gy for the whole liver, 47 Gy for 2/3 liver, 90 Gy for 1/3 liver.²⁹ The same group suggests adapting the given dose individually, accepting a 10% toxicity level calculated by using the Lyman-NTCP model.

Other constraints reported in the literature, show that at least 700/800 ml of the normal liver should

receive a total dose <15 Gy/18 Gy in order to preserve hepatic function.^{22,26}

In case of liver targets, gold fiducials need to be implanted in order to be able to track. This obviously harbours the risk of an invasive procedure, but also the possibility of tumour cell seeding along the needle track. This risk cannot be neglected as shown by reported incidence of seeding (0-12.5%) in other techniques, such as RFA.³⁰

Conclusion

Stereotactic body radiotherapy allows administering ablative doses on liver lesions while sparing the surrounding healthy tissue and minimising the risk of complications. Different groups report high local control rates with relatively low incidence of grade 3 or higher toxicity. Although fiducial implantation is required if one intends to track the lesion in real-time, the robotic radiosurgery approach can be labelled as a non-invasive and yet ablative procedure. According to published data, local control and survival are at least comparable to other available treatment techniques, even to surgery. Safety of the procedure has been demonstrated both for oligometastases in the liver and for HCC. For the latter disease, SBRT can be used as a bridging therapy before liver transplantation or exclusively, if patients are not eligible for surgery. Nowadays, the total dose and the number of fractions are not settled and SBRT still has to be compared to surgery in operable patients in randomized trials. These trials should ideally evaluate the influence on the quality of life and the total cost of stereotactic radiotherapy as well. However, it is a safe and effective treatment in selected patients, if surgery is not an option.

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