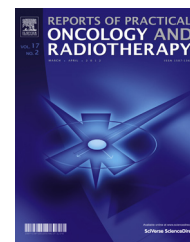


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## Review

# Management of liver cancer. The Surgeon's point of view



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## ABSTRACT

During the last twenty years, a huge progress has been achieved in the treatment of liver cancer and recent strategies include interventional radiology, chemotherapy regimens and surgery. Meanwhile, Stereotactic Body Radiation Therapy (SBRT) has developed in the treatment of all organs with millimetre accuracy, very few side effects and a high control rate. So, SBRT has become a therapeutic weapon in his own right in liver tumour treatment. Many publications have reported encouraging results in colorectal liver metastasis, hepatocellular carcinoma on cirrhosis and peripheric cholangiocarcinoma. It is important that radiation therapists involve systematic multidisciplinary “liver tumour” meetings to discuss therapeutic indications and initiate treatments quickly.

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## 1. Background

Until now, surgery has played a central role in the treatment of liver cancer. Even though for several decades, surgical resection was the only potentially curative option, since 15 years, the therapeutic arsenal has significantly increased. Systemic and local chemotherapy, techniques of thermo ablation and, more recently, stereotactic radiotherapy, have shown encouraging results and are more and more used currently alone or in combination with surgery. At the same time, improvements in the knowledge of liver anatomy and liver function, and development of new surgical techniques allow surgeons to go further and further in terms of volume resected

or biliary and vascular reconstruction. But there are still some limits. In this way, surgery cannot be seen as the only way but as being part of a large therapeutic coordinated group including, oncologists, radiologists, gastroenterologists and radiotherapists. A multidisciplinary approach and adequate therapeutic strategies are now the keys to treat more and more patients in a curative intent.

## 2. Progress in surgery

The respect of some rules and recent advances in knowledge of liver capacities have enabled liver surgeons to treat more

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and more patients and to improve short and long term results after hepatic resection.

### 2.1. Liver anatomy and liver function

Since the description of surgical liver anatomy by Couinaud 60 years ago,<sup>1</sup> a great number of different resection procedures have been described and achieved with very good immediate results<sup>2</sup>: non-anatomical resection, segmentectomy, bi-segmentectomy, major resection and extended major resection. However, some rules must be respected: the future live remnant (FLR) must have an adequate afferent and efferent blood supply, and biliary drainage. Furthermore, the volume of FLR must be sufficient to maintain a liver function during the postoperative period. In case of normal liver function, an FLR of approximately 25–30% is considered to be sufficient to maintain liver function after resection.<sup>3</sup> But for patients with hepatic dysfunction (cirrhosis, severe obstructive jaundice) or earlier liver injury (chemotherapy), a higher FLR of approximately 40% is recommended.<sup>4</sup> A good and simple method to estimate resectability is to estimate FLR to a body weight ratio which should be greater than 0.5.<sup>5</sup> More recently, <sup>99m</sup>Tc-Mebrofenin hepatobiliary Scintigraphy has been used with success to measure FLR function.<sup>6</sup>

### 2.2. Liver regeneration

If a human or an animal can survive to a 70% ablation of the liver, this is due to the unique and remarkable capacity of regeneration. In a few weeks, the volume of FLR is restored. When liver hypertrophy is required preoperatively (portal embolization of a hemi-liver), it has been shown that the FLR increases from 10 to 46% after a period ranging from 2 to 8 weeks.<sup>7</sup> But in some cases of underlying pathology (cirrhosis) or early hepatic toxicity (alcohol abuse, viral infection, chemotherapy), the capacity of liver regeneration is decreased. This must be taken into account to stop toxic agents, to plan the time of operation and the extent of the procedure.

### 2.3. “Secondary resectability” concept

In a significant number of cases, whatever the pathology, a liver tumour can be considered as unresectable at the time of diagnosis. The best example is given by colorectal liver metastasis. Using the multidisciplinary approach, we can stretch the limits of resectability. Thus, when the FLR is too small, we can induce hypertrophy by portal vein embolization or portal vein ligation or a combination of portal vein ligation and parenchymal transection.<sup>8</sup> When the tumour volume is too important, some inductive chemotherapy regimens can induce a secondary resectability in more than half of cases.<sup>9</sup> When the disease is bilobar, the concept of two-stage hepatectomy can be used.<sup>10</sup>

### 2.4. Technical aspects

The main risk factors of postoperative morbidity and mortality are well known: preservation of blood supply and biliary drainage, limited per-operative and postoperative blood loss and sufficient liver volume remnant. Several different

technical improvements in recent years allow us to achieve these main objectives.

#### 2.4.1. Pre-operative liver hypertrophy

If the FLR appears to be too small after operation, it is possible to induce hypertrophy of the FLR by embolization or ligation of the portal vein of the contralateral hemi-liver.<sup>7</sup> This practice is widely used and has given excellent results with low morbidity. In some situations, hypertrophy must be obtained very quickly; a recent procedure which combines portal vein ligation and parenchymal transection induces significant hypertrophy in one week. Two surgical procedures are requested but in that case morbidity and postoperative mortality are increased.<sup>8</sup>

#### 2.4.2. Vascular clamping

Even if the procedure of vascular clamping is controversial, most of the surgical teams around the world use this manoeuvre. There are several different techniques from occlusion of afferent blood supply of one segment to total vascular exclusion. The most popular and widely used is the “Pringle manoeuvre”.<sup>11</sup> The effect on blood loss is significant and side effects are low.

#### 2.4.3. Central venous pressure

Management of a low central venous pressure is of tremendous importance and limits blood loss during parenchymal transection.<sup>12</sup>

### 2.5. Hanging manoeuvre

It has been understood recently that implementing the liver transection in anatomical position for major hepatectomy is very useful, particularly in the case of big lesions. This represents the concept of anterior approach and hanging manoeuvre.<sup>13</sup>

### 2.6. Vascular and biliary reconstruction

Some very specialized teams, particularly in Asia, have published good results after vascular reconstruction of hepatic arteries, hepatic veins and microscopic biliary reconstructions.<sup>14</sup>

### 2.7. Raw surface management

Hemostasis and biliostasis of the liver raw surface after hepatectomy are essential. Recently, a great number of new devices such as glue, hemostatic compress, coagulation process have become available.<sup>15</sup>

## 3. Limits in liver surgery

In different situations, surgery cannot be applied:

Some patients, for extra hepatic reasons, are not suitable for surgery: the presence of underlying disease such as cirrhosis; planned resection would leave in place less than 30% of liver volume; planned resection would compromise afferent blood supply of the two hemi-livers or compromise afferent blood supply on one side and efferent venous drainage on the

other side; biliary drainage of the future liver remnant would be compromised, too.

In these situations, we need other treatments and a multidisciplinary approach.

#### 4. Multidisciplinary approach: the way to push back and stretch the limits

When surgery alone is unable to be conducted to “in sano” resection (R0), combination of different treatments could be a good option either in the same procedure or in two postponed procedures. The use in the same procedure of resection surgery and ablative therapy as radiofrequency is very common.<sup>16</sup> Thus, radio frequency can treat with curative intent lesions of no more than 3 or 4 cm, deep in the parenchyma and not too close to vascular or biliary structures. Other types of ablative therapy, such as “microwave” or “electroporation”, can treat bigger lesions closer to vascular or biliary structures.<sup>17</sup> When surgery cannot be applied in a patient, other combined treatments have been described: for example in CHC not suitable for surgery, it is possible to combine chemo embolization for downstaging and radiofrequency in a curative intent.<sup>18</sup>

In the next future, one can imagine a place for radiotherapy in this multidisciplinary approach.

#### 5. Place of stereotactic radiotherapy

Until now, external beam radiotherapy has had a very limited place in the treatment of liver cancers. The risk of hepatic toxicity has been considered as very high with “radiation-induced liver disease” represented by hepatitis, fibrosis, cirrhosis and lethal hepatic insufficiency. This risk has been observed with a total dose delivered of 30 greys.<sup>19</sup>

However, it is well known that radiotherapy can induce a very good local control of liver cancer nearly 90% at 1 or 2 years.<sup>20–22</sup>

Technical progress in radiotherapy has recently improved the benefit-risk ratio by optimization of target volumes, protection of normal liver and best management of respiratory moves (gating).<sup>19</sup>

Stereotactic Body Radiation Therapy (SBRT) has the advantage to deliver high doses of radiotherapy to confined areas while sparing toxicity to surrounding structures of liver parenchyma.

Thus, with good efficacy and low toxicity, indications might be extended greatly.

From a surgeon’s point of view, liver SBRT could be indicated in 3 different situations:

- (1) In a palliative intent for a local control of some lesions in patients who are not considered for surgery or ablative therapy as some types of intra hepatic cholangiocarcinoma, hepatocellular carcinoma or colorectal liver metastasis.
- (2) In a multidisciplinary approach, liver SBRT could be used in combined treatments as it is already done for surgery and ablative therapy, provided that radiotherapy and other treatments, such as surgery, cannot be delivered in the

same procedure with the exception of some very specialized centres.

- (3) In a curative intent as neoadjuvant therapy combined with chemotherapy. This is already used in some centres for treatment of selected patients with hilar cholangiocarcinoma combined with surgery or liver transplantation

#### 6. Indications of SBRT according to disease

##### 6.1. Hepatocellular carcinoma on cirrhosis (CHC)

CHC represents a large field of development for radiation therapy. CHC represents 1,000,000 new cases per year worldwide. Fewer than 30% of patients are eligible for currently available curative treatments, namely liver transplant, surgical resection and radiofrequency ablation (RFA) as a result of disease stage, portal hypertension, poor liver function or limited resources in the case of transplantation. Radiation represents an efficient ablative therapy and is an alternative to the existing options. Foreseeable roles for radiotherapy could be:

- (1) Difficult location, e.g. subcapsular location, or tumour located near the vascular structures or biliary system not accessible to classic ablative techniques.<sup>23</sup>
- (2) Size larger than 5 cm in which the risk of local failure for ablative techniques is high.<sup>24</sup>
- (3) Evidence of tumour vascular thrombus in association with Sorafenib.
- (4) Adjuvant treatment after trans-arterial chemoembolization (TACE) in the same way that we use RFA after TACE.<sup>25</sup>
- (5) Bridge to liver transplantation for patients who are above the Milan criteria. For these patients, it has been recently demonstrated that successful “downstaging” could be a good prognosis factor.<sup>26</sup>

##### 6.2. Intrahepatic (IHCC) and hilar cholangiocarcinoma (HCC)

IHCC is a rare tumour with a frequent lymphatic extension, frequent peritoneal spread and large tumours at the time of diagnosis. More than 30% are considered irresectable after morphological evaluation. Furthermore, chemotherapy regimens, such as the association gemcitabine-oxaliplatin (Gemox), have poor results. SBRT has recently shown encouraging results in terms of local control<sup>19</sup> with survival rate without progression of 70% and 35% at 1 and 2 years.

HCC represents a different disease. If peritoneal spread and node involvement are frequent, the specific problem is related to the anatomical situation of the hilum, the frequent vascular encasement (hepatic artery and portal vein) and the tumour progression along the wall of the biliary tree. If there is a local vascular encasement or a bilateral distal biliary extension without peritoneal and node extension, it is still possible to have a curative intent. In this case, after an explorative laparotomy or laparoscopy, which confirm the situation, liver transplantation after neoadjuvant chemo radiotherapy can be undertaken. Several centres have published encouraging results with 70% free-disease survival at 5 years, namely with SBRT and Capecitabine.<sup>27</sup>

A very similar protocol has been recently published in the case of IHCC.<sup>28</sup>

### 6.3. Colorectal liver metastasis

If resection of colorectal liver metastases is still the gold standard, a high rate of patients are not eligible for surgery because of unfavourable tumour factors, difficult location of lesions or poor general condition. Until now, among the other local treatment techniques, RFA is the most widely used. However, RFA is limited to lesions smaller than 3 cm, not too close to major blood vessels or main biliary tree or gallbladder, not too close to the diaphragm or the heart and not subcapsular. In these situations, clearly, SBRT can play a role. Recent study has demonstrated a 2-year local control of 74% with SBRT.<sup>29,30</sup> SBRT is becoming a real alternative to RFA.

Furthermore, one can imagine that it will be possible to combine surgery with SBRT for bilobar lesions not suitable for surgery alone or surgery combined with RFA.

Finally, it has been hypothesized that the combination of radiotherapy and angiogenesis inhibitors may have a synergistic effect offering a new therapeutic prospect.<sup>31</sup>

### 6.4. Other tumours

Indications of surgery and SBRT in other primary or secondary liver tumours are not standardized. Decision must be taken in a “case by case” discussion during a multidisciplinary meeting.

## 7. Conclusion

There is no longer any doubt that radiotherapy and particularly SBRT will play a more and more important part in the treatment of liver cancer. In the same way as the use of radio frequency, the future could combine SBRT and surgery. Liver surgeons are strong supporters of frequent and regular multidisciplinary meetings. In each meeting, several patients discussed should be potentially eligible for SBRT but radiotherapists are not commonly present during a “liver cancer meeting”. If we wish a quick development of radiotherapy in our therapeutic range to face liver cancer, systematic presence of radiotherapists during these meetings might be a real progress.

### Conflict of interest

None declared.

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None declared.

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