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Review article

Stereotactic body radiation therapy for liver tumours

Radiothérapie en conditions stéréotaxiques des tumeurs hépatiques

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ABSTRACT

Recent improvements in radiation therapy delivery techniques provide new tools to treat patients with liver-confined disease, either with hepatocellular carcinoma or liver metastases. An appropriate selection of the patients made during a multidisciplinary specialized tumour board is mandatory. It should be based on the disease extension, an accurate evaluation of the comorbidities and the liver functions. The added value of this approach has to be evaluated in well-designed trials, alone or in combination with other treatments such as surgery, local treatments, chemoembolization and/or chemotherapy with or without targeted agents. Stereotactic body radiation therapy should be applied under strict conditions of expertise of the radiation oncology departments, including equipment and educational training programmes. However under these conditions, preliminary results seems highly encouraging in terms of local control and tolerance but should be confirmed in large controlled prospective trials.

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RÉSUMÉ

Les développements technologiques récents de la radiothérapie lui permettent de disposer désormais de nouvelles modalités permettant de proposer des solutions thérapeutiques nouvelles aux patients atteints de carcinome hépatocellulaire ou de localisations hépatiques secondaires. Une sélection rigoureuse des malades par un comité multidisciplinaire spécialisé en maladie hépatique est nécessaire afin d'apprécier au mieux l'extension de la maladie, les conditions médicales du patient avec sa fonction hépatique et ses comorbidités. La valeur ajoutée de cette approche doit être étudiée en priorité dans des études cliniques contrôlées, seule ou en association avec la chirurgie, les traitements locaux, la chimio-embolisation et la chimiothérapie avec ou sans thérapie ciblée. Ces traitements doivent être appliqués dans des conditions strictes d'expertise des services qui les proposent, portant autant sur l'environnement technologique que sur la formation des équipes. Néanmoins, à ces conditions, les résultats préliminaires sont encourageants aussi bien en termes de contrôle local que de tolérance. Ils doivent être validés dans des études prospectives appropriées.

1. Introduction

Hepatocellular carcinoma accounts for 80–90% of primary liver cancer. It is becoming the fifth most common cancer and the third most common cause of cancer-related death in the world [1].

With no specific treatment, the prognosis is very poor, and the median survivals for patients with early and advanced tumours are 6–9 months and 1–2 months, respectively. Several

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Table 1
Summary of dose–volume constraints for the liver.

Study	Dose–volume constraints reported	Dose–volume constraints converted to V (Gy)
Herfarth et al. [28]	12 Gy to 30% 7 Gy to 50%	V12 ≤30% V7 ≤50%
Schefter et al. [25] Kavanagh et al. [35]	700 cm^3 <15 Gy	V15 ≥700 cm^3
Hoyer et al. [36]	10 Gy total <30%	V10 <30%
Méndez Romero et al. [24]	D33 <21 Gy D50 <15 Gy	V <21 ≤33% V15 ≤50%

treatment modalities are available, including surgical interventions (tumour resection and liver transplantation), percutaneous (ethanol injection, radiofrequency thermal ablation) and transarterial (embolization, chemoperfusion, or chemoembolization) interventions, systemic chemotherapy, and radiation. Although hepatocellular carcinoma is currently known as a radiosensitive tumour, the use of radiotherapy is limited because of the poor radiation tolerance of normal liver to local control doses, and complexity of tumour localization [2].

On the other hand, new radiotherapy techniques, including three-dimensional conformal radiotherapy, stereotactic radiotherapy (SBRT), proton therapy and heavy-ion radiotherapy, allow safe delivery of higher dose external beam radiotherapy to liver tumours and the focus of the treatment has shifted from palliative purposes to cure-oriented therapies. SBRT offers an interesting alternative to invasive management since in selected patients it appears to be a treatment option for patients who are not eligible for surgery or invasive procedures [1,2]. All these approaches can provide comparable outcomes, but pre-existing hepatic dysfunction, lesion size or position can significantly limit the indications with regard to patient eligibility and treatment side effects [3,4].

Since the liver is a common site of inoperable metastases of many tumour types, SBRT may be appropriate for selected patients suffering from “oligometastatic” disease [5].

SBRT is emerging as a new non-invasive treatment in selected patients with either liver-confined metastatic disease or primary liver carcinoma. Lax et al. published the first series of hepatocellular carcinoma patients treated with extracranial radiotherapy, in 1994 [6].

Forty-one patients with hepatocarcinoma (20 tumours, 11 patients) and hepatic metastases (21 tumours, 17 patients) received doses ranging from 15 to 45 Gy in 1 to 5 fractions. Most of them responded to the treatment and showed a good tolerance. They demonstrated that SBRT was feasible and well tolerated by patients. Following these promising initial results, additional reports utilizing SBRT for hepatocellular carcinoma were published (Table 1).

2. SBRT technique

Considering that high doses are delivered in a few number of fractions, the movements of the liver during the treatment have to be taken into consideration [7,8].

In particular, respiration is associated with continuous breathing motion of the liver. The fact that the motion of extracranial targets such as the liver is taken into account during SBRT and the development of image-guided radiotherapy in this field have improved target localization and outcomes. In the definition of SBRT proposed by Timmerman et al., secure immobilization was the first point to ensure optimal treatment delivery [4].

The need for accurate repositioning from simulation to treatment and rigorous compensation for organ motion require control devices such as abdominal compression or breath-hold maneuvers to maintain the tumour in a reproducible stage of the respiratory cycle. In Case’s et al. study, during free-breathing, the average amplitude of liver motion was 1.4 mm in the medial-lateral plane, 9.0 mm in the cranial–caudal plane and 5.1 mm in antero-posterior plane. Inter- and intrafraction variability in liver position in non-breath-hold SBRT lead to geometric uncertainties of no greater than 1 cm in the cranial–caudal plane and 0.5 cm in the axial plane [9]. In most of the series, fiducial markers are implanted under ultrasound evaluation near or around the tumours, at least 2 or 3 gold markers, at the superior and lower cranio-caudal limits of the visible disease. Some authors reported the use during computed-tomography (CT) simulation and treatment delivery of customized, external vacuum-type synthetic body mold from the neck to the pelvis which limited the effects of breathing on liver movement. Others demonstrated the utility of abdominal compression in stereotactic body frame to reduce respiratory tumour motion. However, in the Eccles et al. series, it has been demonstrated that 38% of the patients could not benefit from active breathing control for intolerance, poor reproducibility and communication problems [10].

To account for tumour motion during the respiratory cycle, a real-time position management technique might be of great interest. The patient was scanned using a spiral technique while the respiration signal is simultaneously recorded. Once the images are acquired, they are post-processed into individual 3D image sets according to the respiratory phases. It is important to maintain regular breathing during image acquisition requiring audio or audiovisual breathing-training techniques [11].

For hepatocellular carcinoma, contrast-enhancement is a brief arterial time. Because of fast tumour wash-out, the contrast information provided by 4D CT scan is not accurate enough to delineate hepatocellular carcinoma. Consequently, image fusion with recent MRI by using a rigid fusion procedure is recommended. Fiducials already placed around the target contributed to the accuracy of the fusion process. The gross target volume (GTV) was delineated on a contrast-enhanced treatment planning CT scan. It included the tumour in all phases of the normal respiratory cycle. To delineate the internal target volume (ITV), the GTV was expanded manually using data provided by the 4D CT scan showing fiducials motion and tumour position in different phases of the respiratory cycle. An additional margin has to be added to the ITV to obtain the planning target volume (PTV) [8,12].

Intensity-modulated radiotherapy (IMRT) has been introduced in the stereotactic irradiation treatment. Volumetric modulated technique or RapidArc have already been shown to be feasible and to improve dosimetric features compared with 3D conformal radiation therapy and with conventional IMRT. But while the treatment dose is optimized and calculated on a static CT image, in lung tumours, the motion of the target in conjunction with the motion of the MLC may result in the delivered dose deviating from the planned dose. Some authors have highlighted this issue and the dosimetric impact of leaf interplay with breathing-induced tumour motion. Even though the reported differences were not significant when RapidArc was delivered with two different arcs and within a single-fraction plan [13]. One study concluded that the interplay between the motion of the leaves and the motion of the target might induce an error in the delivered dose [14]. Recently, Wang et al. demonstrated in 22 patients treated with RapidArc using Free Flattening Filter condition that the prescribed dose to the targets as well as the dose delivered to the organs at risk respected all the constraints in a prospective dose-escalation study [15].

Radiation centres using CyberKnife® to treat hepatocellular carcinoma reported their results. A series from Cárdenes et al. found 100% local control after 36 to 48 Gy in 3–5 fractions [16]. In a retrospective study, Choi et al treated 32 patients. Doses ranged from 30 to 36 Gy in 3 fractions. One-year local control and survival were respectively 72 and 81%. A recent French retrospective study from