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Original article

Robotic stereotactic body radiation therapy for tumours of the liver: Radiation-induced liver disease, incidence and predictive factors

Radiothérapie stéréotaxique des métastases hépatiques et des hépatocarcinomes : hépatopathie radio-induite, incidence et facteurs prédictifs

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ABSTRACT

Purpose. – Robotic stereotactic body radiation therapy is a new option to treated unresecable liver tumours. The objectives were to assess the tolerance of this technique, to identify predictive factors for toxicity and evaluate the efficiency of this treatment.
Patients and methods. – From June 2010 to November 2012, robotic stereotactic body radiation therapy was proposed for 56 patients with unresecable hepatocellular carcinomas (23 patients) or hepatic metastases (41 patients). Two or less hepatic lesions, lesion size under 75 mm and WHO score under 3 were selection criteria. The prescribed dose was 45 Gy/3 fractions or 60 Gy/3 fractions. The primary end-point was toxicity, using the radiation-induced liver disease definition and to identify predictive factors. Secondary end-points were in-field local control and overall survival.
Results. – The median follow-up was 12.5 months. The one-year local control rate and the one-year overall survival rate were 64% [CI95%: 48.2 to 76.5%] and 89% [CI95%: 76 to 95%], respectively. For patient treated with a total dose of 60 Gy, no one experienced recurrence. According to the definition we took, radiation-induced liver disease rate was 0 or 9%. A lesion size at least 35 mm was a predictive factor to liver toxicity ($P = 0.01$).
Conclusion. – Using robotic stereotactic body radiation therapy, the incidence of radiation-induced liver disease is weak and spontaneously reversible. Prospective studies are required to put in evidence other predictive factors of radiation-induced liver disease and confirm the optimal dose treatment.

Mots clés :
Hépatocarcinome
Tumeurs du foie
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Toxicité hapatique

RÉSUMÉ

Objectifs de l'étude. – La radiothérapie stéréotaxique robotisée est une nouvelle option pour le traitement des tumeurs du foie non résécables. Les objectifs étaient d'évaluer la tolérance de cette technique, en se focalisant sur l'hépatopathie radio-induite, d'identifier des facteurs prédictifs de toxicité et d'évaluer l'efficacité de ce traitement.
Patients et méthodes. – Entre juin 2010 et novembre 2012, la radiothérapie stéréotaxique robotisée a été proposé à 56 patients atteints de carcinomes hépatocellulaires (23 lésions) ou de métastases hépatiques (41 lésions). Les critères de sélection étaient la présence d'une ou deux lésions hépatiques, une taille lésionnelle totale inférieure à 75 mm et un score selon l'OMS de moins de 3. La dose prescrite était 45 Gy ou 60 Gy en trois fractions. L'objectif principal était l'évaluation de la toxicité, en se focalisant sur l'hépatopathie radio-induite et d'identifier des facteurs prédictifs. Les critères secondaires étaient l'évaluation du contrôle local et la survie globale.

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Résultats. – Le taux de contrôle local à un an et celui de survie globale à un an étaient respectivement de 64 % [intervalle de confiance à 95 % : 48,2–76,5 %] et 89 % [76–95 %]. Toutes les tumeurs traitées à la dose totale de 60 Gy étaient contrôlées. Les taux d'hépatopathie radio-induite, incluant ou non comme critère une élévation supérieur à trois fois la normale des gamma glutamyl transférases, étaient respectivement de 9 et 0 %. Une taille des lésions de 35 mm ou plus apparaissait comme un facteur prédictif de toxicité ($p = 0{,}01$).
Conclusion. – En utilisant de la radiothérapie stéréotaxique robotisée, l'incidence d'hépatopathie radio-induite est faible et spontanément réversible. Des études prospectives sont nécessaires pour mettre en évidence d'autres facteurs prédictifs de toxicité hépatique et déterminer la dose et le fractionnement optimal.

1. Introduction

Stereotactic body radiation therapy is both an alternative and a complementary technique to hepatic surgery, radiofrequency ablation and chemoembolization [1,2] for treating hepatocellular carcinoma and hepatic metastases. Several studies have suggested the feasibility of stereotactic body radiation therapy and have shown encouraging results [1–6]. Since June 2010, an image-guided system delivering hypofractionated robotic stereotactic body radiation therapy (Cyberknife®, Accuray Incorporated, Sunnyvale, California, USA) is available in our radiotherapy unit. Radiation induced liver disease is a common toxicity in conformational radiotherapy, but it has not especially study in stereotactic body radiation therapy. The main objective of this retrospective study was to assess the tolerance of this technique using the radiation induced liver disease rate and to identify predictive factors for toxicity. The secondary aim was to evaluate the efficiency of this treatment.

2. Patients and methods

2.1. Patients

Between June 2010 and November 2012, a robotic stereotactic body radiation therapy was proposed for patients with hepatocellular carcinoma or hepatic metastases, who were ineligible for hepatic surgery, radiofrequency ablation or chemoembolization. All of the 56 patients were treated at the Oncology-Radiotherapy Department, Henry S. Kaplan Cancer Center, CHRU Tours, France.

For the 21 patients with hepatocellular carcinomas (23 lesions), selection criteria were: WHO score under 3, Child-Pugh score under C (16 cirrhotic patients, 12 with A and 4 with B Child-Pugh score), one or two hepatic lesions, lesion size under 70 mm.

For the 35 patients with hepatic metastases (41 lesions), selection criteria were: WHO score under 3, controlled extra hepatic disease, two or less hepatic lesions, lesion size under 75 mm. Colorectal adenocarcinoma was the main primary tumor (23 patients). The others were lung (four patients), breast (two patients), head and neck (two patients), pancreas (two patients) and esophagus (two patients).

All patients were French, over 18 years old, and informed consent was obtained from each patient included in the study before treatment. All cases were discussed and validated in a multidisciplinary proceeding.

Thirty-seven males and 19 females, with a median age of 69.5 years old (range: 32 to 87 years old) were involved. Thirty-four patients were in a prior treatment failure and all were ineligible to a validated therapy. The median hepatic volume was 1380.4 cm^3 (range: 795.4 to 3200.9 cm^3), the median longest diameter of lesions was 25.5 mm (range: 9 to 72 mm), 23 mm (range: 14–60) for hepatocarcinomas and 27 (range: 9–72) for hepatic metastases. Patient characteristics are shown in Table 1.

2.2. Planning and treatment

For each patient, two to six gold fiducials were implanted, close to the lesion, with a CT scan control, under local anesthesia. One patient did not have gold fiducials implantation because of ascites. Three patients have been treated two times; the same gold fiducials have been used for the second treatment. A median time of 13 days (range: two to 104 days) following gold fiducials implantation, a 1 mm slice thickness triphasic (arterial phase, portal phase and late phase) planning CT scan was recorded. The CT scan was merged on the gold fiducials with a hepatic MRI. The median time between planning CT scan and beginning of treatment was 12 days (range: two to 45 days). The median overall treatment time was 5.5 days (range: three to 13 days).

Dosimetry and treatment were performed using the Multiplan® v3 treatment planning software (Accuray Incorporated, Sunnyvale, CA), the Synchrony® Respiratory Tracking System (Accuray Incorporated, Sunnyvale, CA) and tracking the tumor lesion in real time on the fiducial markers.

The gross tumour volume (GTV) was delineated based upon the best acquisition of image, either the contrast-enhanced planning CT or MRI. The clinical target volume (CTV) consists of the GTV with an expansion of 5 mm in the liver (CTV = GTV + 5 mm) to treat any microscopic disease extension. The planning target volume (PTV) was obtained by an expansion of 3 mm around the CTV (PTV = CTV+ 3 mm) to take into account the secondary uncertainty to the slice thickness. The prescribed dose to the 85% isodose line was either 45 Gy (49 patients, 87.5%) or 60 Gy (seven patients, 12.5%), in three equal fractions. Due to the well tolerance at the dose of 45 Gy, we started to raise the dose to 60 Gy. Dose constraints are shown in Table 2. Median GTV was 20.6 cm^3 (1.3 to 144.8 cm^3) and median PTV was 48.7 cm^3 (10.1 to 246.3 cm^3). Treatment characteristics are shown in Table 3.

2.3. Follow up

All patients have a clinical examination, a liver function test (including total bilirubin, ASAT, ALAT, GGT, PAL) and a contrast enhanced CT scan of the thorax, the abdomen and the pelvis, at the beginning of the treatment. The clinical follow up consist of a first examination at 6 weeks, then every three months. Liver function tests were done every 15 days during the first three months, then every month until they return to normal. Imaging was repeated at each follow up every three months (contrast-enhanced CT scan, MRI or PET-scan). Patient treated for hepatocarcinomas had a diagnosis and a radiological follow-up by MRI. Contrast-enhanced CT scan was used for the follow-up of patients with hepatic