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SBRT in liver cancer

Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma

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ABSTRACT

Purpose: To describe efficacy and safety of stereotactic body radiation therapy (SBRT) for the treatment of inoperable hepatocellular carcinoma.
Methods: The records of 77 consecutive patients treated with SBRT for 97 liver-confined HCC were reviewed. A total dose of 45 Gy in 3 fractions was prescribed to the 80% isodose line. Local control (LC), overall survival (OS), progression-free survival (PFS) and toxicity were studied.
Results: The median follow-up was 12 months. The median tumor diameter was 2.4 cm. The LC rate was 99% at 1 and 2 years. The 1 and 2-year OS were 81.8% and 56.6% respectively. The median time to progression was 9 months (0–38). The rate of hepatic toxicity was 7.7% [1.6–13.7], 14.9% [5.7–23.2] and 23.1% [9.9–34.3] at 6 months, 1 year and 2 years respectively. In multivariate analysis, female gender (HR 7.87 [3.14–19.69]), a BCLC B-C stage (HR 3.71 [1.41–9.76]), a sum of all lesion diameters $\geqslant$2 cm (HR 7.48 [2.09–26.83]) and a previous treatment (HR 0.10 [0.01–0.79]) were independent prognostic factors of overall survival.
Conclusion: SBRT allows high local control for inoperable hepatocellular carcinomas. It should be considered when an ablative treatment is indicated in Child A patients.
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Hepatocellular carcinoma (HCC) is the most frequent primary hepatic tumor, developing in 90% of the cases with advanced cirrhosis [1]. In France and in the USA, the incidence is low (age-standardized rates of 6.56/100.000 and 6.12/100.000 respectively) compared to that in Eastern Asia. However, the mortality rate in France, with 5.67/100.000 inhabitants is the second highest in developed countries after Japan.

Surgical resection is the standard of care for solitary liver-confined HCC and orthotopic liver transplant provides the best long-term survival, as it treats both cancer and the underlying cirrhosis [2,3]. For inoperable tumors, radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) are the recommended curative treatments, while transarterial chemoembolization (TACE) is mostly regarded as palliative [4]. Radiotherapy is not described as an efficient and validated treatment for HCC [5]. Conventional radiotherapy was associated with high rates of liver toxicity and low efficacy but 3D conformal radiotherapy showed encouraging results [6,7].

The first results for stereotactic body radiation therapy (SBRT) in hepatic tumors were published by Blomgren et al. in 1995 [8]. We started treating hepatic tumors in 2007, as we participated in a prospective medico-economic study on SBRT led by the French national cancer institute (Inca).This retrospective study presents the outcomes of patients treated for liver-confined HCC in our institute.

Methods and materials

Patients

A review was conducted from the data of all the patients treated with SBRT for a localized HCC, from July 2007 to October 2013 in our center.

Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; RECIST, response evaluation criteria in solid tumors; CTCAE, common terminology criteria for adverse events; LC, local control; OS, overall survival; PFS, progression-free survival; BCLC, Barcelona clinic liver cancer; RFA, radiofrequency ablation; TACE, transarterial chemo-embolization; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; OAR, organs at risk; RILD, radiation induced liver disease; CT, computed tomography; CLIP, cancer of the liver italian program; MELD, model for end-stage liver disease; AFP, alfa-foeto protein; TTP, time to progression; mRECIST, modified response evaluation criteria in solid tumors.

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The eligibility criteria for the treatment were: an Eastern Cooperative Oncology Group (ECOG) score inferior or equal to 2, less than 3 synchronous lesions, inoperable tumors (patient unfit for surgery or tumor-related contraindication), a maximum tumor diameter inferior to 6 cm, a Child-Pugh (CP) score ranging from A5 to B8. The HCC diagnosis could be histological or according to the American Association for the Study of Liver Diseases (AASLD) radiological criteria [4]. Previous treatments were accepted.

Previous to treatment, every patient underwent either an abdominal spiral CT scan or a hepatic multiparametric MRI (fat-saturated T2-weighted, gradient echo fat-saturated T1-weighted and gadolinium-enhanced dynamic multiphase sequences) and a complete blood work, including alpha fetoprotein measure.

All cases were presented in a multidisciplinary liver tumor board, including hepatologists, hepatic surgeons, radiation oncologists and radiologists. All patients signed an informed consent to be treated. This study was approved by our institutional research ethics committee and by the French computer watchdog (CNIL).

Treatment

Seven to ten days before the planning CT scan, 2–4 fiducial markers were implanted next to the lesion under sonographic or CT guidance [9]. A personalized vacuum mattress-type contention device allowed patient immobilization in supine position. Planning CT scan included 2 acquisitions of 1 mm-thick slices, 40 and 70 s after contrast agent injection.

Gross Tumor Volume (GTV) was defined as the arterial enhancing lesions with wash-out on the delayed phase. Delineation was facilitated by image fusion approach, using pre-treatment MRI. The Clinical Target Volume (CTV) was obtained adding 5–10 mm isotropic margins to the GTV. The Planning Target Volume (PTV) corresponds to the CTV with 2–4 mm isotropic margins. CTV and PTV margins were chosen mostly according to the size and visibility of the target on the planning CT.

Organs at risk (OAR) included whole liver, healthy liver (liver minus GTV), stomach, duodenum, kidneys, spinal cord, heart, lungs and bowels. Table 1 presents dose–volume constraints to OAR.

Total dose was 45 Gy in 3 fractions, prescribed to the 80% isodose, encompassing PTV. Treatment was performed twice a week, for a total duration of 6–10 days. Dosimetric constraints to OAR relied on QUANTEC recommendations for 3 fractions SBRT [10–12]. Treatment was performed by Cyberknife® (Accuray Inc, Sunnyvale, USA), delivering 6 MV photons. Synchrony® system was used, allowing real time target tracking.

Table 1
Dose–volume constraints to organs at risk.

Organs at risk	Constraints
Liver	D33% < 21 Gy
	D50% < 15 Gy
Kidneys (Left + Right)	D35% < 15 Gy in 3 fractions
Left or right Kidney (single)	V15 < 33%
Heart	D_{max} 30 Gy
Stomach	D_{max} 24 Gy
	D5 cc < 21 Gy
Duodenum	D_{max} 24 Gy
	V15 Gy < 5 cc
Small intestine	V27 Gy < 0,5 cc
	V16 Gy < 5 cc
Large intestine	V30 Gy < 1 cc
	V27 Gy < 20 cc
Medullar spine	D_{max} < 18 Gy
Lungs (Left + Right)	V20 < 20%
	V10 < 30%

Patient follow-up

Patients had an evaluation every 3 months on the first year after treatment and every 6 months thereafter. Follow-up included clinical examination, contrast-enhanced MRI (or CT scan when MRI was not feasible) and blood work. Acute toxicity was defined as adverse events occurring within 3 months after the end of the treatment and late toxicities as events occurring after 3 months, and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Classic and non-classic Radiation induced liver disease (RILD were defined according to QUANTEC 2010 [11,13]. We defined hepatic toxicity as the first occurrence of classic or non-classic RILD or ascites anytime from the treatment.

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was used to assess radiographic tumor response. Progression was also assessed on MRI or CT-scan and included metastatic progression, infield progression (occurring within the PTV) and outfield progression (intrahepatic recurrence outside the PTV).

Statistical analysis

Quantitative variables were described by median and range and qualitative variables by frequency and percentage.

Overall survival (OS), progression free survival (PFS) and hepatic toxicity were studied and the following prognosis factors were investigated: gender, age, TNM class, CP score, previous treatment, ECOG score, BCLC score, CLIP score, OKUDA score, number of lesions, MELD score, initial AFP, PTV/healthy liver ratio, sum of the GTVs, sum of the lesions diameters. More factors were tested for hepatic toxicity: total irradiation time, mean irradiation time per fraction, number of beams, mean dose to the liver, liver volume receiving 10 Gy (V10 Gy), 15 Gy (V15), 21 Gy (V21) and 30 Gy.

OS and PFS were described using the Kaplan–Meier method. The prognostic value of each factor was studied using bivariate Cox proportional hazards model and the results were expressed with the hazard ratio (HR) and its 95% confidence intervals. The validity of the Proportional Hazard (PH) assumption was checked using the Scaled Schoenfeld Residuals [14]. The parameters with a p-value less than 0.5 in bivariate analysis were introduced in a multivariate Cox proportional hazards regression, with both backward and stepwise selection.

Hepatic toxicity was measured from the end date of radiotherapy to the date of last follow-up and was described by the cumulative incidence method since death was considered as a competing risk [15]. We used proportional subdistribution hazards regression method proposed by Fine and Gray to investigate each prognostic factor [16]. The parameters with a p-value less than 0.2 in bivariate analysis were introduced in a multivariate regression based on the same method. The final multivariate model was assessed with a backward selection.

All statistical analysis was performed by means of SAS software (SAS Institute Inc., Cary, NC 25513). P-values <0.05 were considered statistically significant.

Results

Patient and treatment characteristics are summarized in Table 2. All seventy-seven consecutive patients were included in the study, with a median follow-up of 12 months. Sixty-one patients had a single lesion, 8 had 2 synchronous lesions. Four patients were treated for 2 metachronous lesions and 4 patients were treated for 2 synchronous lesions and a third metachronous lesion. A total of 97 lesions were treated. Only 12 patients had received a previous treatment on the target. A total dose of 45 Gy in 3 fractions was prescribed to 87 lesions (89.7%), otherwise dose and fractionation were adapted to match OAR constraints.