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Review

Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review

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ABSTRACT

This paper aimed to review the literature concerning the use of proton therapy systematically in the treatment of hepatocellular carcinoma, focusing on clinical results and technical issues. The literature search was conducted according to a specific protocol in the Medline and Scopus databases by two independent researchers covering the period of 1990–2012. Both clinical and technical studies referring to a population of patients actually treated with protons were included. The PRISMA guidelines for reporting systematic reviews were followed. A final set of 16 studies from seven proton therapy institutions worldwide were selected from an initial dataset of 324 reports. Seven clinical studies, five reports on technical issues, three studies on treatment related toxicity and one paper reporting both clinical results and toxicity analysis were retrieved. Four studies were not published as full papers. Passive scattering was the most adopted delivery technique. More than 900 patients with heterogeneous stages of disease were treated with various fractionation schedules. Only one prospective full paper was found. Local control was approximately 80% at 3–5 years, average overall survival at 5 years was 32%, with data comparable to surgery in the most favorable groups. Toxicity was low (mainly gastrointestinal). Normal liver $V0_{Gy} < 30\%_{volume}$ and $V30_{Gy} < 18–25\%_{volume}$ were suggested as cut-off values for hepatic toxicity. The good clinical results of the selected papers are counterbalanced by a low level of evidence. However, the rationale to enroll patients in prospective studies appears to be strong.

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Primary liver cancer is the third most prevalent cause of death from cancer worldwide [1], with a growing incidence in Europe and in the United States in the last decades [2]. Hepatocellular carcinoma (HCC) represents 90% of all liver cancers. In most cases, HCC is associated with an underlying chronic liver disease developed in the presence of well-known risk factors such as viral hepatitis, alcohol abuse and exposure to aflatoxin.

Cancer progression, mainly loco-regional progression is the cause of the majority of deaths in HCC population [3]; indeed, the rate of extrahepatic metastases is limited even in patients with advanced, unresectable HCC [4].

Therefore, a strong rationale exists for the improvement of loco-regional therapies in HCC patients. Early stages can be treated with a curative approach; local control (LC) and prolongation of survival are the goals in the treatment of advanced HCCs.

Surgery (resection or liver transplantation) achieves the best outcomes in the treatment of HCC, with a reported rate of survival greater than 70% at 5 years in selected series [5]. However, the percentage of HCC patients suitable for surgery is limited by both tumor and patient related contraindications.

Other therapeutic approaches for localized HCC consist of ablation with percutaneous ethanol injection (PEI) or, more recently, radiofrequency ablation (RFA) [6]. However, the occurrence rate in the ablation site is not negligible, especially for tumors larger than 3 cm [7]. Transarterial chemoembolization (TACE), a non-curative treatment with a positive impact on survival [8], is considered the strategy of choice for multinodular HCCs, which corresponds to intermediate Stage B disease according to the commonly adopted Barcelona-Clinic Liver Cancer staging system [9].

Localized cancers at other sites greatly benefit from radiotherapy, which is currently a robust competitor of surgery in several oncological diseases. In the context of HCC, radiotherapy has a narrow therapeutic window due to 1) the low-radio-tolerance of the liver and 2) the need for high doses of radiation for disease control. Irreversible hepatic failure can occur as a consequence of radiation- induced liver disease (RILD) [10].

Recent advances in radiotherapy delivery techniques could help to enlarge the therapeutic window for HCC, allowing for a better

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tailoring of the dose distribution on the target volume while improving the sparing of nearby tissues. Several studies have demonstrated that partial hepatic RT with X-rays is feasible, resulting in promising responses in unresectable HCC patients [11,12].

Nevertheless, the possible role of external radiotherapy in HCC treatment is still under debate: the recently published guidelines of the European Association for the Study of the Liver and of the European Organisation for Research and Treatment of Cancer (EASL-EORTC) on the management of HCC briefly stated that "no evidence to support" the use of external radiotherapy for the treatment of HCC exists, and encouraged "further research testing modern approaches" [13]. Conversely, among the National Comprehensive Cancer Network (NCCN), guidelines indicate that radiotherapy (hypofractionated, stereotactic radiotherapy or conformal radiotherapy with conventional fractionation) could represent an alternative to ablation/embolization for unresectable HCC [14].

In the context of radiation therapy, proton therapy (PT), due to its unique dosimetric characteristics (i.e., a finite range in tissue along with a near zero dose beyond the end of its path), could be an excellent option for the treatment of this disease.

In general, comprehensive reviews concerning the use of PT in cancer revealed a potential benefit for HCC patients. Some limitations of these reviews with respect to the selection of the HCC studies should be noted: only one paper was identified in the review of Olsen et al. [15], while the three studies retrieved by De Ruysscher et al. [16] came from a single Institution (Tsukuba, Japan) and presented an overlap in the population of the included patients, which might be a confounding element for the data analysis.

In light of these limitations, the present study aimed to systematically review the role of PT in the treatment of HCC while focusing on the following objectives:

- to define its effectiveness and safety;
- to register the currently adopted delivery techniques;
- to address the specific technical issues regarding the use of protons in the treatment of HCC.

Materials and methods

All aspects relative to the research questions were identified and formulated in a specific protocol approved by all the authors (supplementary appendix).

The literature search was limited to English language papers and carried out in the Medline and Scopus databases on December 2012 for the period 1990–2012. The electronic database search was performed independently by two researchers (FD and LW) plus one additional researcher to settle any possible disputes (MA). The following search terms and their combination were employed: "proton therapy OR hadron therapy OR particle therapy OR charged particle therapy" AND "hepatocellular carcinoma OR hepatoma OR primary liver cancer OR HCC." The reference list of selected studies was also screened for other eligible studies. In addition, a manual search was performed that focused on the abstracts of meetings of the American and the European Societies of Therapeutic Radiation Oncology (ASTRO, ESTRO), the Particle Therapy Co-operative Group (PTCOG) and the American Society of Clinical Oncology (ASCO) annual congresses for possible inclusion of supplementary studies.

The study eligibility criteria included papers reporting outcome and/or toxicity for HCC patients treated with PT. Studies reporting patients treated with carbon ions or other heavy particles were excluded. Studies reporting technical issues were included if they referred to a population of patients actually treated. Experimental studies as well as plan comparisons studies were excluded. Data are reported according to the PRISMA guidelines [17].

According to the report eligibility criteria, any type of study could be accepted with the exception of single case reports. To avoid overlap of the patient populations, which could bias the results of the review, only the most updated population was included in the review if multiple series referred to the same population of patients.

Results

Literature search results

A total of 324 citations were retrieved to be screened for eligibility. The entire process of review (Fig. 1) led to a final set of 16 studies to be included in the review: seven studies reported clinical outcomes [18–24], five works dealt with technical issues [25–29], while three analyzed potential predictors of treatment-related toxicity [30–32] and the last study reported both clinical outcomes and an analysis of liver function after PT [33].

The most relevant data that originated from the clinical studies that were not presented as a full paper [22–24] were reported in the supplementary appendix (Table 1A).

Several studies from Tsukuba, Hyogo and Kashiwa were retrieved during the review process; both overall clinical results, concerning the use of PT for HCC, and the outcomes of specific subgroups of patients were reported (supplementary appendix Table 2A). Two studies were published from Kashiwa, Japan, the former in 2005 [34] and the latter in 2011 [33]. Only the more comprehensive papers were considered to comply with the inclusion criteria.

Clinical studies

The clinical experience (five full papers) originated from the following PT centers: the Proton Medical Research Center (PMRC, Tsukuba, Japan), the Hyogo Ion Beam Medical Center (HIBMC, Tatsuno, Japan), the National Cancer Center Hospital East (NCCHE, Kashiwa, Japan), and the Loma Linda University Medical Center (LLUMC, Loma Linda, USA).

Four retrospective studies and one prospective study were retrieved. Table 1 shows the main relevant clinical inclusion criteria of the selected studies along with the relevance of both the studies design and their clinical findings according to the classification system developed by the National Cancer Institute.

Proton delivery techniques and treatment planning procedures

The main technical characteristics of the selected studies are detailed in Table 2.

Patient population

More than 800 HCC patients received PT in the studies reported as a full paper. The main characteristics of patients included in the selected studies are illustrated in Table 3 (full volume table is reported in the supplementary appendix).

Treatment regimens and clinical results

A description of the various treatment schedules adopted by the selected studies along with the main results in terms of clinical outcome are provided in Table 4 (full volume table is reported in the supplementary appendix).

Briefly, the LC and OS at 5 years were 86.9% and 23.5%, respectively, in the first report from Tsukuba [19]. In the second report from Tsukuba a 5-year survival of 55.9% was registered for Child-Pugh (CP) A disease, which was significantly higher than the 44.5% survival at 5 years reported for Child-Pugh B patients.

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