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Proton Therapy Results in the Treatment of Hepatocellular Carcinoma According to the Barcelona-Clinic Liver Cancer (BCLC) Staging System

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Abstract

Proton therapy represents the most advanced form of radiotherapy currently available. Hepatocellular carcinoma (HCC) has been extensively treated with proton therapy since 1983 with encouraging results in terms of effectiveness and safety, as reported in recent research articles, systematic reviews and meta-analyses. In this report, we summarized for the first time the results of proton therapy treatment for HCC according with respect to the Barcelona Clinic Liver Cancer Staging System, the most adopted classification system for HCC which provides information on both prognostic prediction and treatment allocation.

Keywords

Proton Therapy, HCC, BCLC Staging System

1. Introduction

Hepatocellular carcinoma (HCC) accounts for 80%/90% of all primary liver cancers, which represent the second most common cause of cancer-related death worldwide [1]. In the USA, primary liver cancer is a relatively rare tumor; its incidence, however, has been rising on average 4.1% each year over the last 10 years [2]. A certain level of hepatic impairment (cirrhosis) is common in most patients.

Despite the several treatment options available for HCC, overall 5-year survival is below 20% [2]. Nevertheless, localized, early stage cancer can be offered a curative approach, which essentially consists in surgery (re-

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section or liver transplantation) or tumor ablation [3].

The use of radiotherapy in the treatment of HCC is not recognized as a standard of care worldwide; it is generally considered as an alternative to ablation/chemoembolization for unresectable HCC in USA and Asia [4] [5], whereas European guidelines are hesitant to include radiotherapy as a treatment option for this disease [6] due to the lack of high level evidence and the risk of potentially lethal treatment related liver toxicity.

However, relatively modern irradiation techniques such as stereotactic body radiotherapy (SBRT) allow for delivering high doses to the tumor target with reasonably low doses to the surrounding liver and other nearby healthy tissues. The results in terms of local control and toxicity reported by several phase I and II studies are encouraging [7] [8]. Moreover, a randomized phase III study evaluating the survival benefit of SBRT in addition to the current standard of care for unresectable HCC is currently ongoing (NCT01730937).

Proton therapy (PT) represents a unique method to deliver radiotherapy which exploits the physical properties of protons of a finite range in tissue to ensure low entrance dose and quasi-zero dose beyond the end of their path [9]. These properties are particularly suitable for HCC treatment, where the therapeutic window is narrowed by the need of a high radiation doses for tumor control in the context of a cirrhotic liver, whose tolerance to radiation is low [10].

It is estimated that more than 50 PT facilities will be active worldwide at the end of 2014 [11].

As of HCC treatment, the first clinical results came from the University of Tsukuba, Japan, (PMRC) where clinical application of PT started in 1983. Up to date, six Centers reported the results of the use of PT for HCC patients: the main clinical results reported in literature are summarized in **Table 1**. PT was considered a well-tolerated treatment in all the reported series; skin-dermatological and gastrointestinal toxicity represented the most frequent reported adverse events.

The outcomes of almost 1000 patients have shown the effectiveness and safety of PT for HCC patients.

During the thirty-year experience of PT treatment for HCC, several treatment schedules were developed and delivered to a heterogeneous group of patients (*i.e.*: various staging and liver functionalities).

The Barcelona-Clinic Liver Cancer (BCLC) Staging system [12] was firstly proposed in 1999 and it represents the most adopted classification system for HCC. Compared with other HCC staging systems, it represents an evolving system that links tumor stage with treatment strategy in a dynamic manner. It offers a prognostic stratification of patients with HCC (**Figure 1(a)**). It divides patients into five stages (0, A, B, C, D) according to pre-established prognostic variables, and allocates therapies according to treatment related status. Further refinements in class stratification or treatment allocation resulting from positive end-trials are expected in the following years. It has been endorsed by both the European and the American Association for the Study of the Liver [6] [13].

In this report, we attempted to summarize the clinical results for patients treated with PT according to the BCLC Staging system (**Figure 1(b)**).

2. Very Early-Early Stage

BCLC Stage 0 or A (Single or Multiple HCC ≤ 3, Performance Status = 0)

Early stages can be offered curative options such as hepatic resection, liver transplantation or tumor ablation.

Chiba *et al*. [14] reported a 5-year survival of 53% for patients with Child Pugh (CP) A patients with solitary-tumor treated with PT at PMRC. Komatsu *et al*. [15] from Hyogo, Japan (HIMBC) analysed the outcome of 343 patients treated with proton (n. 242) or carbon ion (n. 101) therapy in the period 2001-2009. A 5-year overall survival of 80.8% and 52.7% for BCLC stage 0 and A patients was reported, respectively. A comprehensive review from Tsukuba analyzed the results of HCC patients being treated with PT between 2001 and 2007; most of patients entered three different treatment protocols, depending on tumor location. A 5-year survival of 55.9% was registered for CP A disease, which was significantly higher than the 44.5% survival at 5 years reported for Child-Pugh B patients.The recent phase I dose escalation study by Kim *et al*. [16] reported a 3-year overall survival of 73.3% in the high dose level (72 GyE in 24 fractions). Patients experiencing a complete response (CR) after PT survived significantly longer compared with non-complete responders. CR was achieved in 77% of BCLC stage A patients. Separate survival data according to BCLC stage were not provided.

A phase III study is ongoing with the aim of comparing hypofractionated PT vs radiofrequency ablation in patient with residual-small HCC (NCT01963429).

Table 1. Clinical studies of PT for HCC.

Center (observation period, type of study)	Sub-group main characteristics*	No. of patients*	Treatment regimen	Median FUP (range)	Local Control	Overall Survival	Main Toxicity**
PMRC (1985-2006, R)	HCC >10 cm in maximal dimension	22	47 - 89.1 Gy in 10 - 35 f	13.4 m (1.5 - 85)	87% at 2 y	36% at 2 y	3 liver failures with no evidence of HCC
PMRC (1989-2000, R)	Pts receiving >1 course of PT	27 (68 T)	1st course: median dose = 72 Gy in 16 f, other courses median dose = 66 Gy in 16 f	62.2 m (8.6 - 148.5)	87.8% at 5 y	55.6% at 5 y	2 acute liver failures2 late bile duct stenoses
PMRC (1990-2000, R)	Pts unfit to receive other treatment modalities*** due to coexisting diseases	21	63 - 84 Gy in 13 - 27 f	3.3 y (0.3 - 10.7 y)	93% at 5 y	33% at 5 y	No ≥ G3 toxicities
PMRC (1990-2000, R)	Pts with deteriorated liver function (CP C)	19	50 - 84 Gy in 10 - 24 f of 3 - 5 Gy	17 m (3 - 63)	91% at 17 m	42% at 2 y	No ≥ G3 toxicities No worsening of CP score
PMRC (1991-2005, R)	Pts with PVTT	35	55 - 77 Gy in 10 - 35 f of 2.2 - 5 Gy delivered to PVTT ± primary HCC	21 m (2 - 88)	91% at 2 y	48% at 2 y 21% at 5 y	1 transient late duodenal bleeding, 1 G4 thrombocytopenia
PMRC (2001-2007, R)	Pts with HCC located adjacent to the alimentary tract (within 2 cm)	47	16 pts receiving 72.6 Gy in 22 f, 31 pts receiving 77Gy in 35 f. PTV reduced after 10 - 25 f to avoid excess radiation to the alimentary tract	23 m (2.8 - 52.4)	88.1% at 4 y	34.3% at 4 y	4 ≥ G2 GI toxicities (1surgical intervention required)
PMRC (2002-2004, R)	Pts with HCC located adjacent to PH	52	72.6 Gy in 22 f (3.3 Gy/f)	Not reported	86% at 3 y	45.1% at 3 y 83.9% at 3 y for solitary T, CP A pts	3 G2 skin toxicities
PMRC (2001-2006, R)	Aged pts (≥80 y)	21	various schedules = 60 Gy in 10 f, 66Gy in 22 f, 70 Gy in 35 f)	Not reported	100% at 3 y	OS = 62% at 3 y CSS = 70% at 3y	2 G3 thrombocytopenia
PMRC (2001-2004, R)	Pts with HCC located ≥2 cm away from GI tract and PH	51	66 Gy in 10 f	34 m (1 - 76)	87.8% at 5 y	OS = 38.7% at 5 y CSS = 60.1 at 5 y	No RILD, 3 late rib fractures
PMRC (2001-2007, R)	3 group of pts = (1) peripheral tumors, (2) tumors located near GI tract and (3) tumors near PH	(1) = 104 (2) = 60 (3) = 95	66 Gy in 10 f 77 Gy in 35 f 72.6 Gy in 22 f 7 pts =>1 protocol	Not reported	81% at 5 y (overall)	OS = 48% at 5y PFS = 12% at 5y (overall)	2 G3 acute dermatitis 3 rib fractures 1 G3 late dermatitis 3G3 late GI toxicities
PMRC (1985-1998, R)	Review of all patients treated in the observation period	162	Various schedules = 72 Gy in 16 f, 78 Gy in 20 f, 84 Gy in 24 f, 50 Gy in 10 f	31.7 m (3.1 - 133.2)	86.9% at 5 y for all T	23.5% at 5 y 53.5% at 5 y for CP A and single T	Acute toxicity: 9.7% ↑ transaminase level (autoresolving) Late toxicity: 1.1% Infection biloma 0.5% Biliary duct stenosis 1.1% GI bleeding
PMRC (2001-2007, R)	Review of all patients treated in the observation period	318	Various schedules = 77 Gy in 35 f, 72, 6 Gy in 22 f, 66 Gy in 10 f	19.3 m (1.2 - 63.6)	83.3% at 5 y for peripheral, single T.	44.6% at 5 y for all pts (55.9% at 5y CP A pts, 44.9% CP B pts) P < 0.01	3 (1.2%) G2 GI 1 pt G3 GI (→surgery) 3 rib fractures 28 G2 skin toxicities

Continued

HIBMC (2001-2008, R)	Pts with HCC <5 cm	105	52.8 - 76 Gy in 4 - 20 f	Not reported	92.5% at 3 y	49.1% at 5 y	8 G3 acute toxicities 1 G3 late skin****
HIBMC (2001-2009, R)	Pts with IVCTT	16 (13 pts treated with protons, 3 pts treated with carbon ions)	66 Gy in 10 f = 4pts 60 Gy in 10 f = 4 pts 76 Gy in 20 f = 3 pts 76 Gy in 38 f = 1 pt 56 Gy in 8 f = 1 pt	Not reported	100 % at last FUP****	OS = 61.1% at 1 y OS = 36.7% at 3 y****	1 G2 acute hepatic toxicity 2 G2 acute dermatitis 1 G2 late hepatic toxicity (resolved with conservative management)****
HIBMC (2001-2009, R)	Review of all patients treatedin the observation period	242	Various schedules = 76 Gy in 38 f, 56 Gy in 8 f, 60 Gy in 10 f, 76 Gy in 20 f, 66 Gy in 10 f, 80 Gy in 20 f, 84 Gy in 24 f, 52.8 Gy dpf in 4 f	31 m	90.2% at 5 y for all pts 84.1% at 5 y for T ≥ 5 < 10 cm	38% at 5 y for all pts 67.6% at 5 y for BCLC stage 0-A pts 30.6% at 5 y for BCLC stage C pts	≥G3 late toxicities in 8 pts 1 G4 dermatitis 4 G3 dermatitis 1 G3 biloma 1 G3 panniculitis 1 G3 GI ulcer 1RILD 8 G2 rib fractures
NCCHE (1999-2003, P)	CP A-B, max T size = 10 cm, Multinodular HCCs elegible if 1) a single CTV could be created or 2) lesions far from target controlled by other therapies	30	76 Gy in 20 f	31 m (16 - 54)	LPFR = 96 at 2y	OS = 62% at 3 y DFS 16% at 3 y	8 PHI (4 deaths without recurrence) 1 skin erosion, 1 painful subcutaneous fibrosis
NCCHE (1999-2007, R)	Update of the previous report including patients treated off-protocol	60	Various schedules = 76 Gy in 20 f, 60 Gy in 10 f, 65 Gy in 26 f	43 m (25 - 92)	LPFS at 3 y = 90% (all pts) LPFS at 5 y = 86% (all pts) LPFS at 3 y for pts receiving 76 Gy vs those receiving 62.5 Gy = 97% vs 56% (P = 0.005) 61% radiological CR 1 to 50 m after PT	OS at 3 y = 56% (all pts) OS at 5 y = 25% (all pts)	PHI in 11 pts, all with ICG R15 > 20%, 7 deaths (5 without recurrence) 3 ≥ G2 GI toxicities, 1duodenitis 1colon ulcer, 1esophagitis
LLUMC (1998-2006, P)	Inclusion criteria: <3 lesions, no extra-hepatic spread, no tense ascites	76	63 Gy in 15 f	NA	80% at 5 y	PFS for patients within Milan criteria = 60% at 3y PFS for patients outside Milan criteria = 20% at 3y 70% OS for transplanted pts	5 G2 GI toxicities No RILD
NCC (2008-2011, R)	Pts with PVTT	27	Various schedules = 50 - 66 Gy in 20-22 f	13.2 m (2.4 - 51.7)	LPFS at 2 y = 61.9%	Median OS = 13 m	No ≥ G3 acute and late toxicities 14.5% 1 point increase in CP score 7% late G2 GI toxicities
MGH (2006-2009, P)	Pilot study of respiratory-gated PT for liver tumors	15 (HCC = 11)*****	Various schedules = 45 - 75 Gy in 15 f	69 m for survivors	100% at last FUP	OS at 3 y = 33%	2 G3 hyperblirubinemia 1 G3 gastrointestinal bleed 1 G5 gastrointestinal perforation

Continued

NCC (2007-2010, P)	Phase I dose escalation study, three dose levels, exclusion criteria = tumors in contact with gastrointestinal tissue	27	60 Gy in 20 f (8 pts) (dose level 1) 66 Gy in 22 f (7 pts) (dose level 2) 72 Gy in 24 f (12 pts) (dose level 3)	31 m (5.2 - 63.4)	100%, 86% and 100% in dose levels 1, 2 and 3 respectively CR = 62.5%, 57%, 1% and 100% in dose levels 1, 2 and 3, respectively (P = 0.03)	OS at 3 y 25%, 66.7% and 73.3% in dose levels 1, 2 and 3 respectively (P = NS)	No ≥ G3 acute and late toxicities

Centers' abbreviations NCCHE: National Cancer Center Hospital East, MGH: Massachussets General Hospital See text for other abbreviations. *The studies coming from PMRC, HYMBC and NCCHE present an overlap of patient population between the series; **Toxicity scored according to the National cancer Institute common criteria and to the RTOG radiation morbidity score; ***transarterial chemoembolisation, percutaneous ethanol injection, percutaneous microwave coagulation, radiofrequency ablation; ****Data included both proton and carbon ion treatments. Separate data not provided; *****Data include intrahepatic cholangiocarcinoma and liver metastases, separate data not provided. Abbreviations: R: retrospective, P: prospective, f: fractions, y: years, pts:patients, PVTT: portal vein tumor thrombus GI: gastrointestinal, T: tumor , OS: overall survival, CSS: cancer-specific survival, PH: porta hepatis, CP: Child-Pugh score, CR: complete respone, PR: partial response, IVCTT: inferior vena cava tumor thrombus, LPFR: local progression free rate, LPFS: local progresson free survival, DFS: disease free survival, PHI: proton induced hepatic insufficiency, ICG R15: indocyanine green retention rate at 15 minutes, NA: not available, BED: biologically equivalent dose, RILD: radiation induced liver disease.

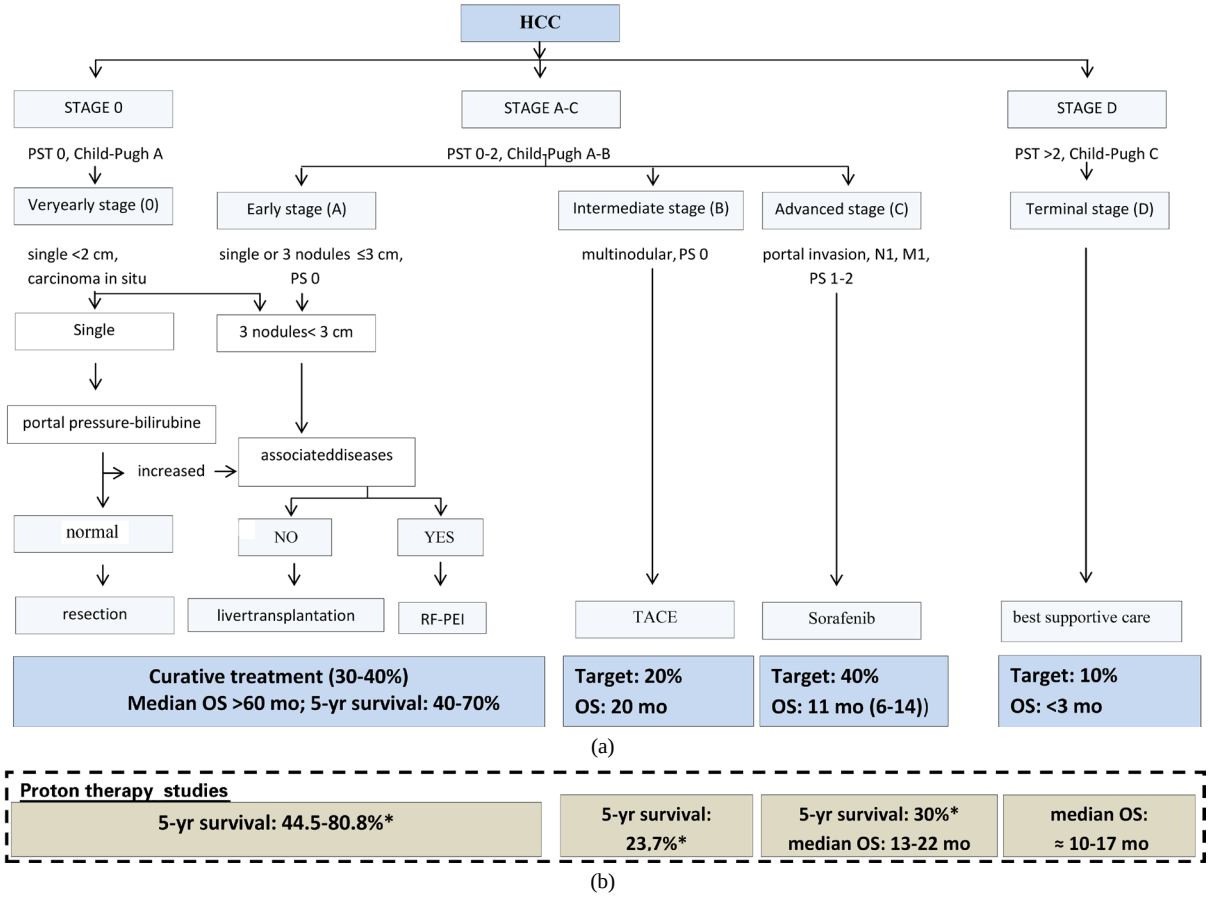

Figure 1. (a) The Barcelona Clinic Liver Cancer Staging System (BCLC) [12]; (b) Summary of Survival data of PT studies according to BCLC stage. Abbreviations: PST, performance status based on Eastern Cooperative Oncology Group score; N, nodal stage; M, metastases stage; RF, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization *including data from carbon ion treatments (see text).

3. Intermediate Stage

BCLC Stage B (Multinodular HCC, Performance Status = 0, Child Pugh = A - B)

The standard treatment option for multinodular HCCs is chemoembolization, a palliative treatment which has

been demonstrated to improve survival compared with placebo in a randomized trial [17]. In the series from Komatsu *et al*. [15] 32 patients in the proton therapy group and 15 patients in the carbon ion arm were staged as stage B. The 5-year overall survival for the whole group was 23.7%. In the study by Kim *et al*. [16], a CR was achieved in 70% of stage B patients.

The Loma Linda University (LLUMC) is currently recruiting HCC patients in a randomized trial of chemoembolization versus PT (NCT00857805).

4. Advanced Stage

BCLC Stage C (Portal Invasion, N1, Performance Status= 1 - 2, Child Pugh = A - B)

BCLC Stage C includes patients with heterogeneous disease related variables which bear a poor prognosis. In this setting, the multikinase inhibitor sorafenib represents the standard of care since its efficacy has been demonstrated in two phase III randomized trials [18] [19].

As of PT, in the series from HIMBC, the 5-year survival for BCLC stage C patients was 30%. In the study by Kim *et al*. [16] four patients were staged as BCLC C: CR rate was 100%.

The use of radiotherapy has shown promising results in case of portal vein tumor (PVT) invasion [20], which represents a poor prognostic factor with limited treatment options.

As of PT, two studies investigated the efficacy of protons in the subset of patients with PVT. Sugahara *et al*. [21] reported a 2-year overall survival of 48% and a median survival of 22 months for 35 patients with PVT treated with PT (median dose 72.6 GyE in 22 fractions) between 1991 and 2005. Interestingly, median survival for patients who received PT for PVT and other active tumors was significantly longer than patients treated with PT for PVT only (26 months vs <10 months). Lee *et al*. [22] retrospectively reported the results of lower doses of PT (median dose 55 GyE in 20 - 22 fractions) in 27 patients with PVT treated with PT at the National Cancer Center, Republic of Korea (NCC) between 2008 and 2011. A median survival of 13.2 months was reported. The 2-year overall survival for patients showing a partial or complete PVT response to PT was 60%.

The role of PT in combination with sorafenibfor advanced stage HCC is currently being evaluated by LLUMC, USA in a randomized trial (NCT01141478).

5. Terminal Stage

BCLC Stage D (Child Pugh C, Performance Status >2)

There is currently no standardized treatment option for Stage D patients apart from best supportive care.

In the series by Komatsu *et al*. [15] 2% of patients in the proton therapy group were staged as BCLC D. Median survival was less than 10 months with no patients surviving more than 36 months.

The prospective phase II study of Bush et al from the LLUMC [23] evaluated the effectiveness of a 15 fraction schedule of PT for HCC treatment; median survival for CPC patients (24%) was 12 months.

Hata *et al*. [24] evaluated the effectiveness of PT in CP C patients treated at PMRC between 1990 and 2000. Among the 197 HCC patients treated with HCC, 19 patients (9.6%) presented with CP C cirrhosis (range 10 - 14). The overall survival at 1 and 2 years were 53% and 42%, respectively; the median survival was 17 months.

6. Conclusions

Recent reviews have investigated the role of PT in the treatment of HCC [25]-[27]. The main findings of these works are that the use of PT for HCC registered impressive clinical results in terms of effectiveness and safety in almost all studies. Prospective data, however, are lacking and cost-effectiveness analyses were not provided. Noteworthy, the amount of clinical data led to the inclusion of HCC among the six disease sites in “Group 1” indications for PT (*i.e.* along with childhood tumors and other clinical conditions that are recommended for coverage by insurance based on existing data) by the American Society for Radiation Oncology (ASTRO) [28].

In this report, we attempted to analyze the results of PT studies for HCC on the basis of the BCLC staging system, the currently most adopted staging system for hepatocellular carcinoma which includes prognostic variables related to tumor status, level of cirrhosis and performance status along with treatment-dependant variables retrieved from randomized trial and cohort studies.

The present analysis was limited basically by three factors: 1) the BCLC score has been rarely reported in the

PT studies (it was used by only two out of the 21 studies summarized in **Table 1**), 2) the attempt to determine the BCLC score on the basis of the patients' characteristics and to correlate it with the reported results was hampered by the lack of comprehensive outcome data (*i.e*. clinical results stratified according to patient's performance status) 3) the low level of evidence of the PT studies weakens the analysis' results.

However, when feasible, the association between BCLC stage and clinical results showed that PT for early stages (0-A) registered survival results which are comparable with the standard curative options.

The survival rates for intermediate and advanced stages (B-C) seem superior to those currently achieved with standard treatments and deserved to be confirmed in larger, controlled trials. Terminal stage was sporadically treated with PT with good results in terms of effectiveness and safety.

In order to allow a direct comparison between PT and current standard of care for HCC, the BCLC Stage should be routinely included in future studies regarding the role of PT in HCC treatment.

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