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Systematic Review

Patient specific outcomes of charged particle therapy for hepatocellular carcinoma – A systematic review and quantitative analysis

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ABSTRACT

Hepatocellular carcinoma (HCC) is a raising condition world-wide. Most of patients are ineligible for surgery at diagnosis due to the advanced stage of the disease or poor medical condition of the patient. Charged particle therapy (CPT) is a radiotherapy modality showing promising results. The aim of this systematic review was to summarize current knowledge on patient-specific outcomes of CPT for HCC, including overall survival, local control, the effect of radiation dose and the toxicity burden. The systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). After comprehensive database search 17 cohorts (16 studies, 1516 patients) were included into qualitative and quantitative analyses; 11 of 16 studies were retrospective. Eleven studies were on protons, 2 studies were on protons and carbon ions and 4 on carbon ions alone, were identified. Median BED10 (biologically equivalent dose) range was 68.75–122.5 GyE. Mean weighted overall survival across studies was 86%, 62%, 59% and 35% at 1, 2, 3 and 5 years, respectively. Mean weighted local control was 86%, 89%, 87% and 89% at 1, 2, 3 and 5 years, respectively. Adjusted morbidity rates were: 54% for acute G1-2 toxicities and 6% for acute ≥G3 toxicities; 9% for late G1-2 toxicities and less than 4% for late ≥G3 toxicities. There was no treatment-associated mortality.

Conclusions: CPT offers high local control, acceptable overall survival and low post-treatment morbidity. Quality of findings, especially on toxicities, is decreased by incomplete reporting and retrospective designs of available studies. Therefore, there is a strong need for better reporting and prospective studies.

Hepatocellular carcinoma (HCC) is a raising condition both world-wide and in Europe, already being one of the leading causes of cancer-specific deaths. Particular characteristics of the disease associated with its location in the liver and mixed etiology remain a challenge. Surgery, both liver resection and liver transplant, is the recommended curative treatment for the eligible patients. However, presence of cirrhosis, localization and extent of the tumor, performance status and comorbidities limit the number of qualifying patients. Moreover, increasing age of patients diagnosed with HCC, further limits the proportion of patients eligible for surgery. Alternative loco-regional treatment modalities either are of established role or are undergoing detailed evaluation in search for their place in HCC treatment algorithms. Thermal ablation (TA), ethanol injections and transarterial chemoembolization (TACE) are treatment modalities recommended by the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for specific stages of HCC [1].

External beam radiation therapy is a relatively novel, non-invasive and promising therapeutic option available in treatment of liver tumors, both primary and secondary [1,2]. This is due to modern treatment planning and delivery techniques, such as stereotactic body radiotherapy (SBRT) as well as emerging modalities such as charged particle therapy (CPT). These approaches enabled limiting treatment toxicity that classically was a major obstacle in liver directed radiotherapy.

CPT encompasses use of different particles. Most frequently used are protons (PBT, proton beam therapy) and carbon ions (CIT, carbon ion therapy). The advantage of PBT is primarily a favorable dose distribution due to the physical properties of protons whereas the biological effects of PBT seem almost equivalent to photons [3,4]. CIT has similar advantageous physical dose distribution [5], but in addition it has potential biological advantages with increased biological effects due to its high linear energy transfer (LET) [6]. CPT may allow sparing organs at risk, especially for the low – and intermediate dose wash [7]. These effects may be

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of particular value in radiation therapy of HCC where the surrounding (cirrhotic) liver is characterized by low radiation tolerance.

While CPT has been used in clinical setting since 1980s, the adoption of this modality has been limited up until recently [8]. This has been, among others, due to technical and financial challenges of building and maintaining accelerators, necessary for this treatment. However, many new facilities, including miniaturized and compact systems, are underway in Europe, USA and Asia thus the availability is improving.

Numerous review articles are available on the topic of CPT for HCC, however only few are systematic [9,10] and only one meta-analysis on CPT is available to date [11]. Summarized data from available trials and retrospective studies on overall survival, local control and toxicity burden are either missing from the literature or available in a limited capacity. Therefore, there is a need for high quality evidence that may be derived from systematic reviews with qualitative analyses. These may be especially useful for experts when coining future guidelines and planning for expansion of CPT capacity. While the overall survival remains the most important outcome for comparisons, it is not the only one of interest. In CPT, potentially low toxicity is of particular importance. This is due to aforementioned unique physical and biological properties, which can potentially prove crucial in limiting the irradiation of the surrounding tissues. Therefore, in this systematic review we aim to summarize current knowledge on patient-specific outcomes of CPT for HCC, including overall survival, local control, the effect of radiation dose and the toxicity burden.

Materials and methods

Search strategy

This review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and facilitated a PICO-styled (Patients, Interventions, Comparisons, Outcomes) research question. PubMed, Scopus, Web of Science and CENTRAL databases were searched for relevant articles. No filters were used.

Evidence acquisition

On the 11th of September 2018 two separate researchers (PS, MA[1]) performed database search to identify studies eligible for the review. Search query was as follows: (proton therapy OR hadron therapy OR particle therapy OR charged particle therapy OR carbon ion) AND (hepatocellular carcinoma OR hepatoma OR primary liver cancer OR HCC). Initial search returned a total of 3063 results. Detailed protocol is presented in PRISMA flowchart (Fig. 1). After screening 64 articles were selected for full text analysis. Forty-eight articles were excluded due to following reasons: full text not in English, full text not available online, case reports, studies including <10 patients, conference papers, abstracts, editorials reporting original data and overlapping study groups. A total of 16 articles reporting a total of 17 cohorts were included in final qualitative and quantitative analyses. Following information was abstracted from the studies: 1st author, date of publication, study design, treatment modality (protons/carbon ions/both), timespan of the study, center treatment was performed in, clinical scenario, number of patients, number of lesions, median size of lesion, percentage of male patients, biologically equivalent dose (BED), total dose and number of fractions, value of assumed relative biological effect (RBE) or assumed RBE model, median follow-up time, overall survival (OS) and local control (LC) at 1, 2, 3, 4 and 5 years, number of acute and late toxicities stratified by grade (G1/2, ≥G3, deaths) according to Common Terminology Criteria for Adverse Events (CTCAE), treatment intent, movement control technique, Child-Pugh Score of patients, performance score according to Eastern Cooperative Oncology Group (ECOG), and number of patients infected with Hepatitis B (HBV) and C (HCV) viruses. If a specific information was unavailable in original manuscript, it is described as Not Reported (NR) in this study. Moreover, acquisition of data on toxicity followed rigorous criteria: if information on specific type of toxicity was missing or presented imprecisely, it was deemed NR. Rate of toxicity equal to zero was considered only if the original study specifically stated that there were no toxicities of a certain type. Data on toxicity were abstracted dividing it into three categories: G1 and G2 toxicities pooled together and described as G1/2 toxicities (mild); G3 and G4 toxicities pooled together and described as ≥G3 toxicities (severe); G5 toxicities (deaths).

Inclusion and exclusion criteria; PICO

This study used a PICO-styled research question to identify studies eligible for inclusion in analysis. Respectively, for Patients: any patients with confirmed HCC of any Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh Score and ECOG scores, with or without previous treatment. All etiologies of HCC were viable for the study; for Interventions: PBT or CIT; for Comparisons: as there is limited amount of studies with controls both studies with and without any comparative were deemed viable; for Outcomes: OS, LC and treatment toxicity should have been reported. Furthermore, if more than one study from the same center with overlapping study timeframes was available, the study with biggest group and/or highest quality of reporting was selected.

Evidence synthesis

Studies included into this review are summarized in Table 1. Total of 16 studies containing reports from 17 cohorts met the inclusion criteria. To analyze findings across studies medians, means, weighted arithmetic means, and standard deviations were used. To assess toxicities a following method was used: all reported toxicities were added up and then divided by number of participants in all studies. This is presented as a value in percentages and called "total percentage" (%tot). However, due to incomplete reporting in original series, another value was calculated: "adjusted percentages" (%adj). In this case total number of toxicities was divided by total number of patients participating in studies that reported the specific toxicity. Toxicities were divided into main categories: liver-related, intestine-related, skin-related, and other (to encompass remaining less common events). Furthermore, we calculated BED10 (α/β = 10 Gy) [12–14]. Calculations were performed using following formula: $(\mathrm{BED}) = n \times d \ (1 + d/\alpha/\beta)$; (n stands for number of fractions; d stands for dose per fraction). All calculations were made using Microsoft Excel 16.17 (Microsoft, Redmond, USA).

Results

General characteristics

Our review included a total of 16 studies, which reported 17 separate cohorts with a total of 1516 patients. Baseline characteristics of the studies are presented in Table 1. There were three types of studies: studies on PBT (studies/patients: 11/1135), studies with mixed groups of patients treated with proton beam or CIT (studies/patients 2/99), and studies on carbon ion therapy (studies/patients: 4/282). One paper by Komatsu et al. reported use of proton beam and carbon ions separately within the original study and therefore was included both into studies on PBT and CIT [15].

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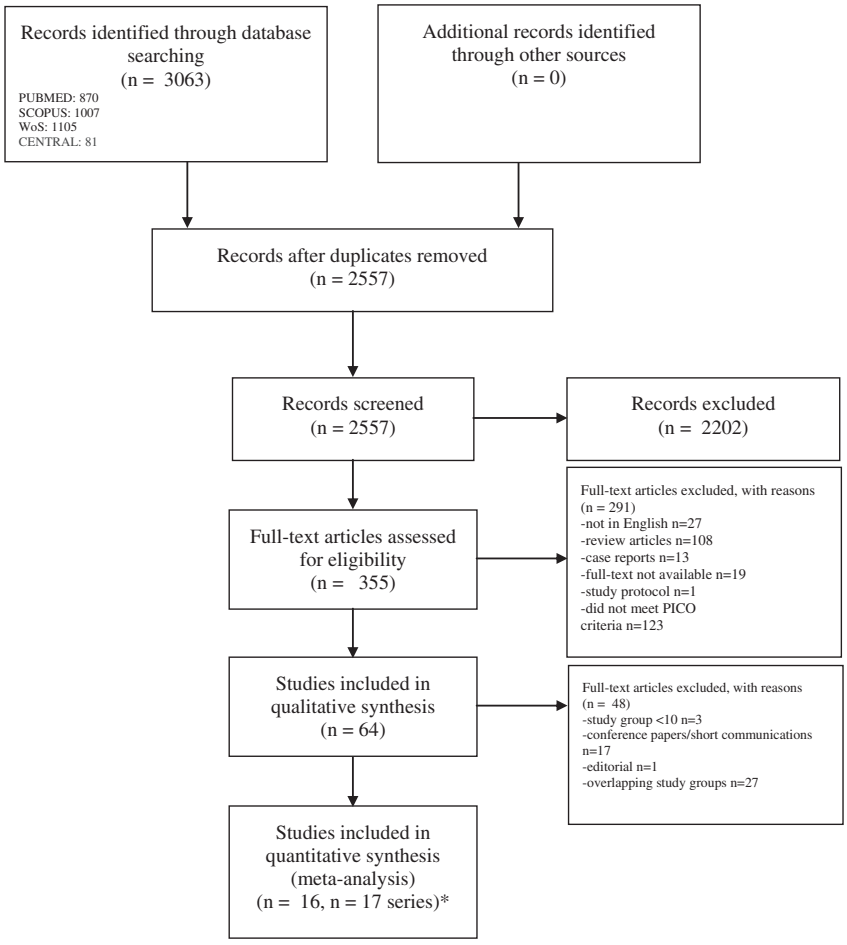

*One study reported two cohorts (a proton- and a carbon ion cohort).

Fig. 1. PRISMA flowchart.

Eleven of included studies were retrospective reports, 2 were prospective reports of phase I/II trials, 2 were reports of phase II trials, 1 was a retrospective study from a prospectively maintained database and 1 was a pilot study. Median share of male sex across the included studies was 75%. Mean lesion number per patient was 1.13 (range 1–1.32) and median lesion size across studies was 47.5 mm (range 25–90 mm). Three recent studies by Yu et al., Mizuhata et al. and Sorin et al. reported on use of CPT for small HCCs (median size 25 mm, 36.5 mm, 30 mm, respectively). In the study by Yu et al. PBT was offered to patients that were ineligible for surgery and Radiofrequency Ablation (RFA) after a multidisciplinary discussion [16]. The study by Mizuhata et al. included patients that were medically inoperable, deemed difficult to control with RFA or did not agree to surgery or RFA [17]. Finally, in the study by Sorin et al. CPT was offered to patients that were either ineligible for surgery and deemed difficult to control with conventional nonsurgical methods (RFA, TACE, ethanol injections) or refused conventional treatment [18]. Median age across studies was 68.5 years. All but 2 studies reported doses in GyE (Gray equivalents), with RBE that was equal to 1.1 for proton studies. For carbon studies patients were treated with use of a variable RBE based on the Kanai semi-empirical model [19]. Four studies did not report RBE value. Median follow-up ranged from 4.9 months to 31.7 months, with median value across studies 23.2 months. Most of the patients underwent previous treatment with median across studies of 70% (range 45–100%). Most frequent previous treatments included TACE and RFA. All studies reported on Child-Pugh Score values. Only 42 (3%) patients included into original studies had Child-Pugh C, while 26% had Child-Pugh B and 72% had Child-Pugh A. Four of 16 studies clearly stated the intent of treatment (curative in 2 cases and mixed in 2). Motion management was reported in 13 of 16 studies. Pencil beam technique was used in at least 2 of the included studies, however, 11 studies failed to report type of treatment delivery. All but 2 studies reported information on numbers of HBV and HCV positive patients, with weighted arithmetic means of infected patients of 20% and 60%, respectively.

Included studies facilitated different fractionation protocols, including SBRT-like protocol with 4 fractions, up to 37 fractions. To enable comparison of different fractionation schemes median BED10 were calculated, as described in methods. Median BED10 across studies was 96.4 GyE (range 68.75–122.5 GyE). In case of 1 study calculation was impossible due to lack of data.

Overall survival and local control

Data on OS and LC were reported in different timepoints: at 1, 2, 3 and 5 years. No study reported OS and LC on 4 years and beyond 5 years. Findings are summarized in Table 2. Data were reported heterogeneously. To summarize findings weighted arithmetic means were calculated. Fig. 2(A and B) represents distribution of weighted arithmetic means of OS and LC, respectively, over time. In included studies CPT offered steady LC at mean level over 85%.

Table 1
Baseline characteristics.

#	Author and year	Enrollment years	Center	Design	Clinical scenario	N of patients	N of lesions	Tumor size[1]	Male %	Age[2]	BED10[3]	Follow-up[4]	Prior treatment[5]
	PBT												
1	Chiba et al. (2005) [21]	1985–1998	PMRC Tsukuba, Japan	R	inoperable	162	192	NR	77%	62.5	118.4	31.7	72%
2	Nakayama et al. (2009) [22]	2001–2007	PMRC Tsukuba, Japan	R	PBT for HCC	318	NR	NR	72%	69	96.6	19.3	100%
3	Komatsu et al. (2011a)* [15]	2001–2008	HIBMC, Japan	R	CPT for HCC	242	278	NR	75%	NR	107.2	31	47%
4	Bush et al. (2011) [23]	1998–2006	Loma Linda, USA	P II	PBT for HCC	76	91	55	70%	62.7	101.3	NR	NR
5	Kawashima et al. (2011) [24]	1999–2007	Kashiwa/ Chiba, Japan	R	inoperable	60	61	45	70%	70	96	NR	60%
6	Lee et al. (2014) [25]	2008–2011	CLC Korea	R	PVTT	27	NR	70	82%	55	68.8	13.2	78%
7	Hong et al. (2014) [26]	2005–2009	Harvard, USA	P II	Respiratory gated PBT	44	58	50	84%	70.5	80.4	19.5	32%
8	Kim et al. (2017) [27]	2012–2015	CLC Korea	R	tumor vascular thrombosis	41	NR	58	85%	55	96	15.2	76%
9	Kimura et al. (2017) [28]	2008–2015	Fukushima, Japan	R	PBT for HCC >50 mm	24	24	90	88%	73	96.6	17.5	NR
10	Yu et al. (2018) [16]	2016–2017	SMC, Korea	P	PBT for HCC	101	>101	25	86%	63	96.3	4.9	96%
11	Mizuhata et al. (2018) [17]	2011–2015	Fukui, Japan	R	HCC adjacent to GI	40	>40	36.5	70%	72	85.9	19.9	90%
	PBT/CIT												
12	Komatsu et al. (2011b) [29]	2009–2011	HIBMC, Japan	R	IVCTT	16	NR	NR	75%	68.5	96	29.6	NR
13	Sorin et al. (2018) [18]	2007–2015	N/R, Japan	P	CPT for HCC	83	>83	30	78%	79	N/A	26.8	67%
	CIT												
14	Kato et al. (2004) [30]	1995–1997	HIMAC/NIRS, Chiba, Japan	P I/II	Cirrhosis/dose escalation	24	27	50	54%	64	93.74	71	75%
15	Komatsu et al. (2011a)* [15]	2001–2008	HIBMC, Japan	R	CPT for HCC	101	108	NR	73%	NR	107.2	31	45%
16	Shiba et al. (2017) [14]	2011–2015	GHMC, Japan	R	Elderly >80	31	34	45	71%	83	122.5	23.2	45%
17	Kasuya et al. (2017) [31]	1997–2003	HIMAC/NIRS, Chiba, Japan	P I/II	dose escalation and hypofractionation	126	133	40	71%	68	102.3	27.1	48%

NR – nor reported; R – retrospective; P – prospective; P I/II – phase I/II trial; P II – Phase II trial; PVTT – portal vein thrombosis; GI – gastro intestinal tract; IVCTT – inferior vena cava thrombosis.
* Study by Komatsu et al. (2011a) contains two patient series reported separately within original study.
[1] Median in mm.
[2] Median in years.
[3] Median in GyE.
[4] Median in months.
[5] Percentage of patients that had prior treatment.

Data on OS show a steady decrease from 86% at 1st year through 62% at 2 and 59% at 3 years to 35% at 5 years.

Relationship between BED10 and OS or LC on 1, 2, 3 and 5 years is presented on Fig. 3(A and B, respectively). Dose escalation seems to improve survival at 1–3 years, while it does not influence survival at 5 years. On the other hand, LC in not substantially influenced by dose escalation.

Toxicity

Data on toxicity were abstracted from original studies and summarized in Table 3. Overall 448 G1-2 and 107 ≥G3 toxicities were reported. This translates to frequencies of 29.6% and 7%, respectively. No treatment-associated death (G5 toxicity) was reported in any of the studies.

Liver toxicities were not common. There were 71 (10.8%) G1-2 and 11 (0.7%) ≥G3 acute liver toxicities. Late liver toxicities were even less common with 15 (1.4%) G1-2 and 11 (0.7%) ≥G3 toxicities.

Across the three main categories of toxicities the most common acute G1-2 were skin-related (7.5%), and least common were intestine-related (2.6%). When adjusting for reporting, myelotoxicities became most common (25.1%) and intestine-related remained least common (4.5%) acute events. Most common late G1-2 toxicities were skin-related (3.3%) and least common were myelotoxicities (0.2%). After adjusting for reporting skin-related remained the most common (4.7%), and liver-related became the least common (1.4%).

In terms of acute ≥G3 toxicities the most common were myelotoxicities (2.6%) and least common were intestine-related (0.13%). After adjusting trend remained the same with 3.8% myelotoxicities and 0.2% intestine related toxicities. Most common ≥G3 late toxicities were myelotoxicities as well (1.3%) and least common were intestine-related (0.3%). Trend remained the same after adjusting with 2.0% and 0.3% toxicities respectively for myelotoxicities and intestine-related toxicities.

Relationship between actual and adjusted toxicities rates was explored by dividing the latter with the prior. Discrepancies ranged

Table 2
Abstracted data on survival and local control.

#	1st Author and year	OS1	OS2	OS3	OS5	LC1	LC2	LC3	LC5
	PBT								
1	Chiba et al. (2005) [21]				24%				87%
2	Nakayama et al. (2009) [22]	90%		65%	45%				
3	Komatsu et al. (2011a)* [15]			59%	38%			91%	90%
4	Bush et al. (2011) [23]								
5	Kawashima et al. (2011) [24]			56%	25%			90%	76%
6	Lee et al. (2014) [25]	56%	33%						
7	Hong et al. (2014) [26]	77%	63%				95%		
8	Kim et al. (2017) [27]		51%						
9	Kimura et al. (2017) [28]		52%				87%		
10	Yu et al. (2018) [16]								
11	Mizuhata et al. (2018) [17]	86%	76%				94%		
	PBT/CIT								
12	Komatsu et al. (2011b) [29]	61%		37%					
13	Sorin et al. (2018) [18]	83%	66%	55%		86%	85%	85%	
	CIT								
14	Kato et al. (2004) [30]	92%		50%	25%	95%	82%	79%	81%
15	Komatsu et al. (2011a)* [15]			59%	36%			91%	93%
16	Shiba et al. (2017) [14]		82%				89%		
17	Kasuya et al. (2017) [31]	90%		50%	25%	95%		91%	90%
	Weighted mean	**86%**	**62%**	**59%**	**35%**	**86%**	**89%**	**87%**	**89%**
	Standard deviation	0.14	0.17	0.08	0.08	0.05	0.05	0.05	0.06

NR – not reported; wAvg – weighted arithmetical mean; SD – standard deviation; OSx – overall survival, where x represents year; LCx – local control, where x represents year.
* Study by Komatsu et al. (2011a) contains two patient series reported separately within original study.

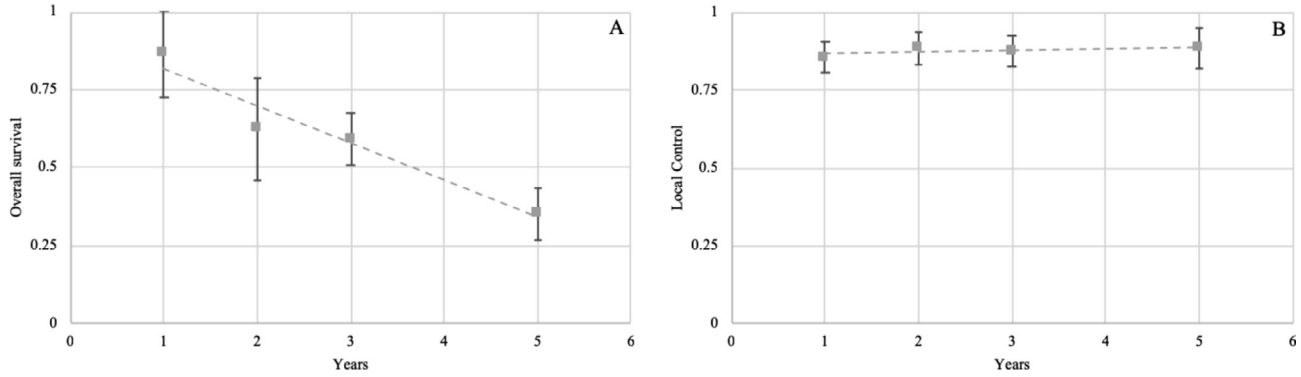

Fig. 2. (A) Weighted arithmetical means of OS from included studies. Error bars represent ± 1SD. (B) Weighted arithmetical means of LC from included studies. Error bars represent ± 1SD.

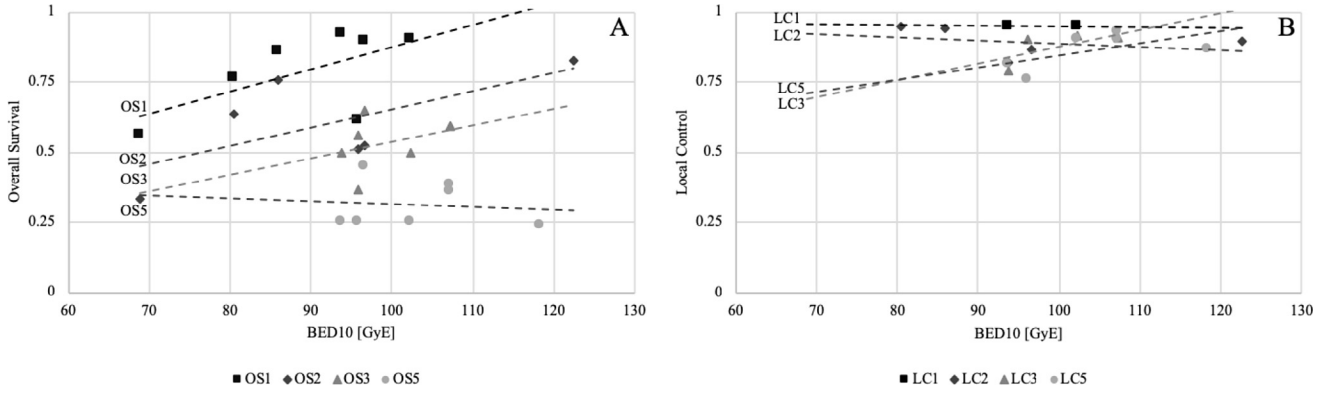

Fig. 3. (A) Overall survival at 1, 2, 3, and 5 years in relationship to increasing BED10. (B) Local control at 1, 2, 3, and 5 years in relationship to increasing BED10.

from 1.05 to 6.68. On average G1-2 toxicities were reported 2.42 times (SD (standard deviation) 1.84) less frequently than expected. Reporting of ≥G3 toxicities was more consistent with those reported 1.36 (SD 0.24) times less frequently than expected. Toxicities such as intestinal, liver-related and skin-related were reported most consistently, while myelotoxicities are reported the least. For example, only 3 studies included information on early G1-2 myelotoxicities, while one of those studies, by Yu et al.,

Table 3
Summarized data on toxicities.

Toxicities										SUM		
	Liver-related		Intestine-related		Myelotoxicities		Skin-related		Other			
	Acute	Late	Acute	Late	Acute	Late	Acute	Late	Pooled	Acute	Late	Pooled[1]
G1-2	71	16	40	28	57	3	114	50	69	282	97	448
≥G3	11	11	2	4	40	20	10	7	2	63	42	107
%tot G1-2	4.68%	1.05%	2.64%	1.85%	3.76%	0.20%	7.51%	3.30%	4.55%	18.59%	6.39%	29.53%
%adj G1-2	**10.84%**	**1.42%**	**4.49%**	**1.94%**	**25.10%**	**0.81%**	**13.23%**	**4.71%**	**6.36%**	**53.65%**	**8.89%**	**68.89%**
%tot ≥G3	0.73%	0.73%	0.13%	0.26%	2.64%	1.32%	0.66%	0.46%	0.13%	4.16%	2.77%	7.06%
%adj ≥G3	**1.31%**	**0.87%**	**0.19%**	**0.27%**	**3.84%**	**2.03%**	**0.96%**	**0.52%**	**0.16%**	**6.30%**	**3.69%**	**10.15%**

G1-2 – pooled grade 1 and 2 toxicities; ≥G3 – pooled G3 and above toxicities; %tot – toxicities as a share in total number of patients; %adj – toxicities as a share in number of patients form studies reporting certain toxicity type.
[1] Pooled: pooled acute, late and other toxicities.

reported 57 cases of such toxicities in 101 patients. Table presenting all of the toxicities reported in original studies is available online in study materials [20].

Discussion

To our knowledge, this is the most comprehensive systematic review on use of CPT in HCC to date. On a robust group of 1516 individuals, our review showed that CPT is a valid option for HCC offering high LC and satisfactory OS at 3 years (87% and 59%, respectively) with low toxicity profile. In particular, liver toxicity was very low (1.3% and 0.9% of G3-4 acute and late events, respectively). These results are comparable or superior when related to other loco-regional treatments such as RFA or SBRT [32–36]. Therefore, CPT is an attractive non-invasive modality in HCC patients with pre-treatment liver dysfunctions or contraindications for surgery.

Our review contains a complete description of reported CPT-related morbidities. Database searches that were performed in preparation of this study revealed over 100 reviews, overviews and editorials, while only 7 of those reported to be systematic reviews. Furthermore, number of review papers is higher than number of original reports available, even if conference papers and articles reporting overlapping cohorts are considered. This proves that there still is lack of quality evidence that could become the cornerstone for planning randomized controlled trials and performing future meta-analyses. It is crucial to fill this gap of knowledge. Currently, radiotherapy is not included in EASL guidelines as standard approach toward the management of HCC with level of evidence: low, and recommendation: weak [1]. The guidelines conclude that despite signs of efficacy and safety there still is a compelling need for large prospective studies, particularly phase II trials, in regards to radiotherapy for HCC [1]. This is due to lack of solid evidence. However, as presented in this review as well as in other systematic reviews and a meta-analysis, results of CPT for HCC are promising. Especially considering that patients with HCC selected for CPT are those usually ineligible for other treatment modalities. This is typically due to the performance status, comorbidities or localization of the tumor. Furthermore, surgery is the only treatment considered as curative and both SBRT and CPT are considered modalities of last resort. As presented in this report, radiotherapeutic options have the potential to become the definitive treatment for patients' ineligible for surgery, once sufficient evidence is present.

Data on overall survival abstracted from original studies are reported in different timepoints. This impairs the possibility of drawing unequivocal conclusions with advanced meta-analytical methods. However, analyses we performed provide some insight into the survival of patients treated with CPT. Survival rates are 86% at 1 year, 62% at 2 years, 59% at 3 years and 35% years at 5 years. These results are comparable with results analyzing patients treated with RFA who had previously received other types of treatment [36]. Furthermore, OS calculated in our study is comparable or superior to reported survivals in SBRT series that are available [33,35]. This is in accordance with findings from a meta-analysis conducted by Qi et al. [11]. It has to be considered, that CPT is more resource consuming in comparison to photon-based radiotherapy. On the other hand, a cost-utility analysis by Leung and Chan suggests, that CPT is, in fact, cost-effective [37].

Analysis of data from original series shows excellent local control, at levels of over 85% over 5 years. While this result is very promising, it is crucial to analyze it cautiously. Local control is calculated only for survivors; therefore, results may be overestimated. While this is a general bias of LC rates it is especially true for HCC, as many patients die due to liver failure which is not necessarily related to treatment or in-field progression of the disease. It is more often due to out-field progression of HCC or progression of underlying liver disease. Furthermore, some patients may be lost to follow-up. Therefore, it is critical that researchers report data on LC along with numbers of patients at risk, at the time of analysis. Nevertheless, LC rates reported in the current study seem to be superior to results reported in SBRT series of HCC patients [32,33].

Reports from original studies usually include total dose and number of fractions. As mentioned, for the comparative purposes we calculated BED. The α/β ratio was considered to be 10 Gy, as it was previously proposed by Shiba et al. [14]. Currently there is no proof that there is a dose-escalation effect for HCC, in contrast to liver metastases [2]. Lack of a LC dose–response relationship is demonstrated on Fig. 3B. However, Fig. 3A (presenting relationship between OS and BED) suggests the opposite. This may be explained by discrepancies in treatment planning for patients with more complex clinical scenarios, such as: tumors' proximity to radiosensitive organs, worse Child-Pugh Score etc. Those patients are both less likely to receive high (i.e. definitive) doses of CPT and *a priori* have an inferior expected survival. This could be a form of selection bias and may potentially explain the counterintuitive findings presented on Fig. 3.

PBT and CIT have significantly distinct RBE. This can potentially lead to differences in outcomes, especially LC and treatment morbidity. Comparison of these two modalities would be of interest. Within this review only 4 CIT cohorts are summarized, therefore such comparison is not feasible. Nevertheless, this is an important future direction in studies on CPT.

Our study shows that CPT is associated with acceptable levels of acute and late toxicities with around 6% of patients experiencing acute ≥G3 toxicities, and less than 4% of patients experiencing late ≥G3 toxicities. In all of the included series, no treatment-related deaths were reported. These results are in accordance to those from a meta-analysis by Qi et al. which analyzed patients treated

with proton and photon based radiotherapy for HCC [11]. Overall, post-treatment morbidity is hard to elucidate, as reporting of acute and late toxicities are often overlapping and not always reported properly. For patients with liver cirrhosis undergoing surgery, post-treatment morbidity is reported at <30% and post-treatment mortality <3% [1]. Results reported in this review may be considered comparable or superior to this data. Moreover, these findings appear to be favorable in comparison to toxicities reported in SBRT series [33,38,39]. This is especially true, when considering that current study presents adjusted rates of toxicities, what not always is the case. Therefore, the benefit of CPT in comparison to SBRT may be even higher.

It is important to consider that reporting of toxicity across original studies does not follow any unified scheme. Although every study adhered to CTCAE in grading toxicities there are major discrepancies in reporting. Usually studies report acute and late toxicities (typical cut-off being 3 months) and G1-G2 (mild) and ≥G3 toxicities (severe). It is typical that G1 and G2 toxicities are summarized within one sentence, that "all G1-2 toxicities were transient and easily manageable" [25,27,29,40]. Underreporting of those toxicities was visible during acquisition of data for this review (see study materials available online [20]) While ≥G3 toxicities reporting is more completely reported, it seems underreported as well. Reporting of toxicity is crucial, especially in studies on CPT. From its physical properties, PCT is expected to be especially superior to photon radiotherapy in treatment related morbidity while comparable in terms of LC and OS. Therefore, it should be reported meticulously to enable possibility of future meta-analyses.

Adjusted percentages for toxicity rates that were calculated for the purpose of this study should be interpreted with caution, as this calculation excludes many studies from the analysis. We believe that those are closer to the actual values and determine the morbidity better than absolute rates of toxicities (or percentages calculated from whole group).

Underreporting of toxicities is more visible in G1-2 than for G3 or higher toxicities. On one hand this is both to be expected and logical, as ≥G3 toxicities are those that actually matter from a physicians' standpoint. On the other, every toxicity represents a burden for the patient and affects his or her quality of life. Toxicities of ≥G3 reported in the analyzed studies are quite low. Therefore, we believe it is feasible to include toxicities of G1 and G2 (especially the latter) into reports, to enable future comparisons of methods.

Interpretation of the data presented in this study should be cautious. This is especially due to the fact that data available in the original studies are incomplete, what may obscure quantitative analyses' results. Most of reported studies have retrospective design, what may especially negatively influence the quality of reporting of adverse events. While 4 studies are prospective trials, those are only phase I and I/II trials. No phase III trial or randomized controlled trial (RCT) was included into our analysis. Database search revealed 2 RCTs (CPT vs TACE) reports: one conference paper and one interim report. However, these were not included as they did not report sufficient amount of data. Furthermore, some studies report mixed groups of patients with different clinical characteristics and provide only pooled data, while other slice databases into multiplicity of small reports. Because of this, in some cases it is hard to elucidate whether articles from the same centers report different or the same cohorts. Study's methods section should clearly indicate whether study group is or is not overlapping with previous reports from the same center. Unfortunately, such information is missing in the original studies. Another important issue arising from analysis of included studies, is the fact that some of them enrolled patients with a relatively low tumor burden who may have potentially been within BCLC criteria for surgical treatment [16–18]. This might have potentially improved the outcome measures we report in this study.

Our study has some important limitations to consider. Firstly, precise acquisition of data was impaired by lacking information on overlapping cohorts, therefore those decisions were based upon information at hand by two separate researchers (PS, MH[2]). Therefore, it is possible that some series that are included are not the best representation of certain centers' experience. Secondly, reporting of data was incomplete. Researchers report data on outcomes with different measures, including OS, PFS, DFS, LC and others and in different timepoints. Moreover, data on PFS and DFS were not abstracted, as these outcome measures are not recommended by the EASL [1]. In consequence, these limitations may decrease the value of conclusions drawn in this study. What is more data from original studies were summarized with very crude statistical methods, such as medians, means and weighted means. Although we believe that employing more advanced statistical methods to incomplete data may only introduce increasing bias and would not be actually informative. Nevertheless, it is our opinion that presented analyses are feasible and informative, especially on the subject of post-treatment morbidity.

Conclusions

In conclusion, we believe that this study provides an important insight into the efficacy and toxicity of treatment with charged particles. CPT offers very promising local control and overall survival and acceptable low toxicity levels that may be more favorable than what has been reported from other radiotherapy modalities. Furthermore, we conclude that research that will be published in the future should be reported more thoroughly, to enable performing meta-analyses.

Contributions

PS designed the study, acquired data, analyzed data, drafted the manuscript and accepted final version. MA acquired the data, reviewed the manuscript and accepted final version. ABS acquired the data, reviewed the manuscript and accepted final version. JK designed the study, reviewed the manuscript and accepted final version. BAJF designed the study, analyzed data, reviewed the manuscript and accepted final version. MH designed the study, analyzed data, reviewed the manuscript and accepted final version.

Disclosures

Authors have nothing to disclose.

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