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SYSTEMATIC REVIEW

Stereotactic body radiation therapy in cholangiocarcinoma: a systematic review

[1]REZARTA FRAKULLI, MD, [1]MILLY BUWENGE, MSc, [2]GABRIELLA MACCHIA, MD, [1]SILVIA CAMMELLI, MD, [2]FRANCESCO DEODATO, MD, [3]SAVINO CILLA, PhD, [4]FRANCESCO CELLINI, MD, [4]GIAN C. MATTIUCCI, MD, PhD, [1]SILVIA BISELLO, MD, [5]GIOVANNI BRANDI, MD, [6]SALVATORE PARISI, MD and [1]ALESSIO G. MORGANTI, MD

[1]Department of Experimental, Diagnostic and Specialty Medicine – DIMES, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy
[2]Radiotherapy Unit, Fondazione "Giovanni Paolo II", Catholic University of Sacred Heart, Campobasso, Italy
[3]Medical Physic Unit, Fondazione "Giovanni Paolo II", Catholic University of Sacred Heart, Campobasso, Italy
[4]Department of Radiotherapy, Policlinico Universitario "A. Gemelli", Università Cattolica del Sacro Cuore, Rome, Italy
[5]Department of Experimental, Diagnostic, and Specialty Medicine, S. Orsola-Malpighi University Hospital, Cancer Research, University of Bologna, Bologna, Italy
[6]Unit of Radiotherapy, IRCCS"Casa Sollievo della Sofferenza" San Giovanni Rotondo, Italy

Address correspondence to: Dr Milly Buwenge
E-mail: *mbuwenge@gmail.com*

Objective Stereotactic body radiation therapy (SBRT) has been used in the treatment of cholangiocarcinoma (CC) but toxicity and clinical results of SBRT in CC are still limited and sparse. Therefore, the aim of this systematic review was to analyze the results of SBRT in the setting of advanced CC.

Methods A systematic literature search was conducted on PubMed, Scopus, and Cochrane library using the PRISMA methodology. Studies including at least 10 patients with diagnosis of advanced CC regardless of tumor site and other treatments were included. The primary outcome was overall survival (OS) and secondary endpoints were local control (LC) and toxicity rates. The ROBINS-I risk of bias tool was used.

Results 10 studies (231 patients) fulfilled the selection criteria and were included in this review. All but one study showed moderate to serious risk of bias. Median follow up was 15 months (range: 7.8–64.0 months). Pooled 1year OS was 58.3% ($_{95\%}$ CI: 50.2–66.1%) and pooled 2 year OS was 35.5% ($_{95\%}$ CI: 22.1–50.1%). Pooled 1year LC was 83.4%, ($_{95\%}$ CI: 76.5–89.4%). The reported toxicities were acceptable and manageable with only one treatment-related death.

Conclusion The role of SBRT in CC is not yet supported by robust evidence in literature. However, within this limit, preliminary results seem almost comparable to the ones of standard chemotherapy or chemoradiation.

Advances in knowledge SBRT seems effective in terms of LC with acceptable treatment-related toxicities. Therefore, SBRT can be considered a therapeutic option at least in selected patients with CC, possibly combined with adjuvant chemotherapy (CHT).

INTRODUCTION

Cholangiocarcinoma (CC) is an uncommon neoplasm representing 3% of gastrointestinal (GI) cancers and the second most common primary liver malignancy.[1] They represent a very heterogeneous group of neoplasm arising from the epithelial cells of the bile duct. CC are classified according to their anatomical location as intra hepatic or extra hepatic. Radical surgery with negative histological margins is the only treatment allowing long-term survival but even after tumor resection, the prognosis is dismal with 5 year overall survival (OS) <20%.[1] Moreover, most of these patients have advanced disease at the time of diagnosis and are candidates for non-surgical treatments. Furthermore, in patients undergoing surgery, 15 to 25% microscopic (R1) or macroscopic (R2) residual disease was reported.[2]

Some studies have demonstrated that external beam radiotherapy (EBRT) with or without systemic chemotherapy (CHT) is a treatment option in unresectable or R1-R2 residual CC with median OS ranging between 10 and 15 months.[3–5] Furthermore, a significant correlation between radiotherapy (RT) dose and OS has been reported.[6–8] However, the possibility to deliver very high RT dose on this site is limited by the low radiation tolerance of both liver and GI tract.

In the last decade, technological improvements in EBRT delivery accuracy and in respiratory motion compensation has enabled the widespread implementation of stereotactic body radiation therapy (SBRT). Particularly, due to its ability to deliver a high and focused dose in few

fractions, SBRT has been proposed for GI tumors of the upper abdomen.[9–12] In particular, this technique could be promising in the setting of locally advanced CC given the close proximity to radiosensitive organs. Whereas high level studies in this field are justified, we believe that a review of the available evidence can be useful for the design of these trials. Therefore, this systematic review aimed at analyzing the results of SBRT in CC by reviewing the available data from clinical outcome studies.

METHODS AND MATERIALS

Our systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) on March 2017 (Registration Number: CRD42017058929).

Bibliographic search

We conducted a systematic search based on PubMed, Scopus, and Cochrane libraries from the earliest data to May 15, 2018. The following search strategy was used on PubMed: stereotactic (All Fields) AND ["human body" (MeSH Terms) OR ["human" (All Fields) AND "body" (All Fields)] OR "human body" (All Fields) OR "body" (All Fields)] AND ["radiotherapy" (Subheading) OR "radiotherapy" (All Fields) OR ["radiation" (All Fields) AND "therapy" (All Fields)] OR "radiation therapy" (All Fields) OR "radiotherapy" (MeSH Terms) OR ["radiation" (All Fields) AND "therapy" (All Fields)] OR "radiation therapy" (All Fields)] AND ["cholangiocarcinoma" (MeSH Terms) OR "cholangiocarcinoma" (All Fields)] OR "Klatskin Tumor" (MeSH Terms).

Inclusion criteria

Human studies of any design (prospective or retrospective) with at least 10 enrolled patients with diagnosis of CC and treated with SBRT were included regardless of the tumor site. Studies on hepatocarcinoma were not excluded if they reported differentiated data on at least 10 CC patients. Only studies published in English language were considered in this review. No restrictions about total delivered dose, Biological Effective Dose (BED) and SBRT technique were imposed.

Outcome measures

The primary outcome was OS. Secondary outcomes were local control (LC) and treatment-related toxicity.

Study selection and quality assessment

We used the PRISMA guidelines as a guide to select the items to be included in the review.[13,14] The title, abstract, and keywords of the identified articles were independently analyzed by two researchers (RF, GM) and disagreements were resolved by a third senior researcher (AGM). Potentially eligible studies were retrieved and full-text evaluation was performed based on the inclusion and exclusion criteria by two different authors (MB, SB) with disagreements resolved by consensus-based discussion. The following data were collected independently by two authors (RF, MB) from each article with disagreements resolved by the senior author (AGM): authors name and year of publication, study design, accrual period, patients and tumor features, other treatments before and after SBRT, technical components of treatment planning and delivery, total dose and fractionation, BED, outcomes, and toxicity. In the studies where BED was not reported, the value was calculated according to the following equation BED = d *[(1 + (d/n ÷ α/β)], assuming an α/β ratio of 10 for the tumor (n= number of fractions, d = total dose).[15] Papers were evaluated based on the ROBINS-I Risk of Bias tool.[16] Two reviewers (RF, MB) assessed the quality of the included studies and discrepancies were resolved on agreement.

Statistical analysis

1 year, 2 year OS, and 1 year LC percentages were pooled by means of a random effects model in case of heterogeneity across studies; otherwise, a fixed-effect model was used.[17] Statistical heterogeneity was estimated with the I^2 statistic (high heterogeneity level:>50%) and tested using the Q2 test (statistical significance level: $p < 0.1$). The survival percentages were reported as estimates and 95% CI.The analysis was performed with MedCalc statistical software (MedCalc®, Ostend, Belgium).

RESULTS

10 articles[18–27] fulfilled the inclusion criteria for this review. A detailed analysis of these studies is reported in Tables 1–3 while in Figure 1, the flowchart of the systematic literature search process is represented. Nine studies were retrospective[18–26] and one was a prospective Phase I study.[27] No randomized controlled trial was found. All but one were considered to have moderate to serious risk of bias according to the ROBINS-I tool.[17] Supplementary Material 1 shows the overall risk of bias rating *per* study according to ROBINS-I.

Characteristics of patients and SBRT technique

Patients' median age ranged from 57 to 72 years.[18–27] The studies were heterogeneous in terms of tumor features, treatment aim, treatment planning, delivery devices, and techniques. Patients underwent SBRT for unresectable or recurrent CC in nine studies[18–27] except for two patients in the study of Mahadevan and colleagues who underwent post-operative SBRT for positive surgical margins.[20] In two studies also patients with liver and/or distant metastases were included.[23,27] Liver transplant after SBRT was performed in 16.0 and 50.0% of patients in two series.[19,21] Two studies included only extra hepatic CC,[21,25] three studies only intra hepatic CC,[18,23,27] and five studies included both anatomical sites.[19,20,22,24,26] Biliary stenting was performed in five series with percentage of patients ranging from 38.2 to 100%.[19–21,25,26] Neoadjuvant CHT was administered in six studies[19,20,22–25] and adjuvant CHT was prescribed after SBRT in two series.[23,24]

Respiratory motion management and image-guided RT were used in all studies[18–27] with large variability among centers. This variability influenced the Planning Target Volume (PTV) definition which resulted heterogeneous. The PTV was not specified in one study.[20] In four studies the PTV was defined as Gross Tumor Volume (GTV) plus 3–5 mm[18,23,25,27] and as Internal Target Volume (ITV) plus 2–8 mm in four studies.[19,21,22,24]

Table 1. Characteristics of the studies included in the systematic review

Study	Study design	Accrual period	No of patients	Median follow up (months)	Tumor features %	Biliary stent %	Treatment	
							Before SBRT %	After SBRT %
Barney et al. 2012[24]	Retrospective	2009–2011	10	14	Intra hepatic: 60.0; extra hepatic: 40.0; primary: 50.0; recurrence: 50.0;	NR	Surgery: 50.0; CHT: 40.0; EBRT: 10.0	CHT:40.0
Ibarra et al. 2012[23]	Retrospective	2001–2010	11	7.8	Intra hepatic: 100; M1: 45.5	NR	Surgery: 50.0; RFA: 27.3; CHT: 45.5	NR
Jung et al. 2014[22]	Retrospective	2005–2013	58	10	Intra hepatic: 57.0; extra hepatic: 43.0; primary: 48.0; recurrence: 52.0	NR	EBRT(40–63 Gy): 15.5; surgery: 51.7	NR
Kopek et al. 2010[26]	Retrospective	1999–2006	27	64	Extra hepatic (Klatskin): 96.0; intra hepatic: 4.0	100	NR	NR
Mahadevan et al. 2015[20]	Retrospective	2006–2014	34	38	Intra hepatic: 73.8; intra hepatic +extra hepatic: 21.4; extra hepatic: 4.8; primary: 85.3; positive margin: 5.9	38.2	Chemoembolization: 2.9: surgery: 5.9	CHT (Gemcitabine or Gemcitabine + cisplatin)
Polistina et al. 2011[25]	Retrospective	2004–2009	10	35.5	Extra hepatic:100; N+: 60.0	100	CHT (Gemcitabine): 100	CHT: 100 (Gemcitabine)
Sandler et al. 2016[19]	Retrospective	2008–2015	31	11.5	Intra hepatic: 19.0; extra hepatic: 81.0 primary: 87.0; recurrence: 13.0; N+: 6.0	NR	EBRT: 6.4; surgery: 3.2; surgery +CHT: 3.2	Liver transplant: 16.0
Shen et al. 2017[18]	Retrospective	2009–2012	28	16	Intra hepatic: 100	No	Chemoembolization: 28.6	NR
Tse et al. 2008[27]	Phase I	2003–2006	10	17.6	Intra hepatic: 100; N+ :60.0; M1: 40.0	NR	Surgery: 10.0 CHT: 40.0	NR
Welling et al. 2014[21]	Retrospective	NR	12	14	Extra hepatic: 100	100	No	CHT (Capecitabine) liver transplant: 50.0

CHT, chemotherapy; EBRT, external beam radiotherapy; M, male; N+, positive lymph nodes; NR, not reported; RFA, radiofrequency ablation;SBRT, stereotactic body radiation therapy.

Table 2. Technical components of treatment planning and dose delivery

Study	Respiratory motion control/ IGRT	Target definition (median tumor volume)	Dose prescription	Median dose (Gy)/fr	BED_{10Gy} (median)	TDT weeks
Barney et al. 2012[24]	4D CT/yes	PTV: ITV + 5 (79.1 cc)	NR	55/5	115.5	1
Ibarra et al. 2012[23]	Yes/yes	PTV: GTV + 3–5 mm (80.2 cc)	To 70% isodose line	30/3	60	2
Jung et al. 2014[22]	Abdominal compression device/ yes	PTV: ITV + 2–4 mm (40.0 cc)	To 70–80% isodose or 92–99% to cover at least 95% of the PTVs.	45/3	112.5	NR
Kopek et al. 2010[26]	Abdominal compression device/ yes	PTV: CTV + 5 mm radial direction +10 mm CC direction (NR)	To the isocenter	45/3	112.5	5–8 days
Mahadevan et al. 2015[20]	Tracking (two gold fiducials) /yes	NR (63.8 cc)	To 75% isodose line	30/3	60	1
Polistina et al. 2011[25]	Tracking/yes	PTV: GTV + 3 mm (NR)	To 80% isodose line	30/3	60	3 days
Sandler et al. 2016[19]	4D CT free breathing/yes	PTV: ITV + 5–8 mm (59.3 cc)	PTV $D_{min} \geq 95\%$ of the prescription dose	40/5	72	1
Shen et al. 2017[18]	Tracking/yes	PTV: GTV + 5 mm (267.4 cc)	PTV $D_{min} \geq 95\%$ of the prescription dose	45/3	112.5	1
Tse et al. 2008[27]	Exhale breath hold/ yes	PTV: GTV + 8 mm (172 cc)	NR	36/6	57.6	2
Welling et al. 2014[21]	Active breathing control/yes	PTV: ITV + 5–8 mm (NR)	Isodose surface covering 99.5% of PTV	50–60/3–5	100–180	2

BED, biologically effective dose;CTV, clinical target volume; GTV, gross tumor volume; IGRT, image-guided radiotherapy; ITV, internal target volume; NR, not reported; PTV, planning target volume; TDT, treatment delivery time; fr, fraction.

The Clinical Target Volume (CTV) to PTV margin was 5 mm radially and 10 mm craniocaudally in one study.[26] The median tumor volume reported in seven studies ranged between 40.0 and 267.4 cm^3 (median: 79.1 cm^3).[18–20,22–24,27] Dose prescription methods and total dose/fraction were highly variable.[18–27] Median prescribed SBRT dose ranged between 30 and 60 Gy in 3 to 5 fractions. Median computed BED ranged between 57.6 and 180.0 Gy. Different dose prescription modalities were reported in eight studies.[18–23,25,26] In four studies, the dose was prescribed to ≥70% isodose.[20,22,23,25] In one study, PTV dose was not less than 95% of the prescribed dose[18] and in another series the dose was prescribed to the isodose covering at least 99.5% of the PTV.[21] In one study, 95% of the PTV received the full prescribed dose[19] and in another study the dose was prescribed to the isocenter.[26] Table 2 reports in details the technical characteristics of treatment planning and delivery.

Outcomes

Overall survival

Median follow up was 15 months (range: 7.8–64.0 months).[18–27] Median OS ranged from 10.0 to 35.5 months (median: 15 months). From nine studies,[18–24,26,27] the pooled 1 year OS in 204 patients was 58.3% ($_{95\%}$Confidence Interval (CI), 50.2–66.1%) with very low heterogeneity between studies (Q^2 test: $p = 0.22$; $I^2 = 24.8\%$) (Figure 2). The pooled 2 year OS reported in five studies[18–20,22,24] (161 patients), was 35.5% ($_{95\%}$CI, 22.1–50.1%) with very high heterogeneity between studies (Q^2 test: $p = 0.0075$; $I^2 = 71.3\%$) (Figure 3). According to the anatomical location of CC, 1 year OS was 57.1% (range: 45.0–58.0%), 81.5% (range: 80.0–83.0%), and 58.7% (range: 45.0–73.0%) in studies including intra hepatic CC, extra hepatic CC, and both sites, respectively.[18–27]

Local control

LC was reported in six studies.[18–20,22,24,26] Data reported in four studies[19,20,22,26] on 123 patients yielded a pooled rate for 1 year LC of 83.4% ($_{95\%}$CI, 76.5–89.4%) with low heterogeneity level (Q^2 test: $p = 0.5514$; $I^2 = 0.00\%$) (Figure 4). The highest value of 100% was reported as crude rate with a median follow up of 14 months.[24]

Toxicity

Acute toxicity was reported in all studies[18–27] and late toxicity in nine series.[18–20,22–27] One study used a non-validated toxicity scale,[21] one study reported overall toxicity not specifying both type and grade[23] while one study did not describe separately acute and late toxicity.[18] Severe acute toxicity (≥G3) was recorded in four studies[19,21,26,27] as cholangitis (50%),[21] abnormal liver enzymes (range: 20.0–55.5%),[26,27] duodenal obstruction (3.2%),[19] pain (7.4%),[26] and transient biliary obstruction (20%).[27]

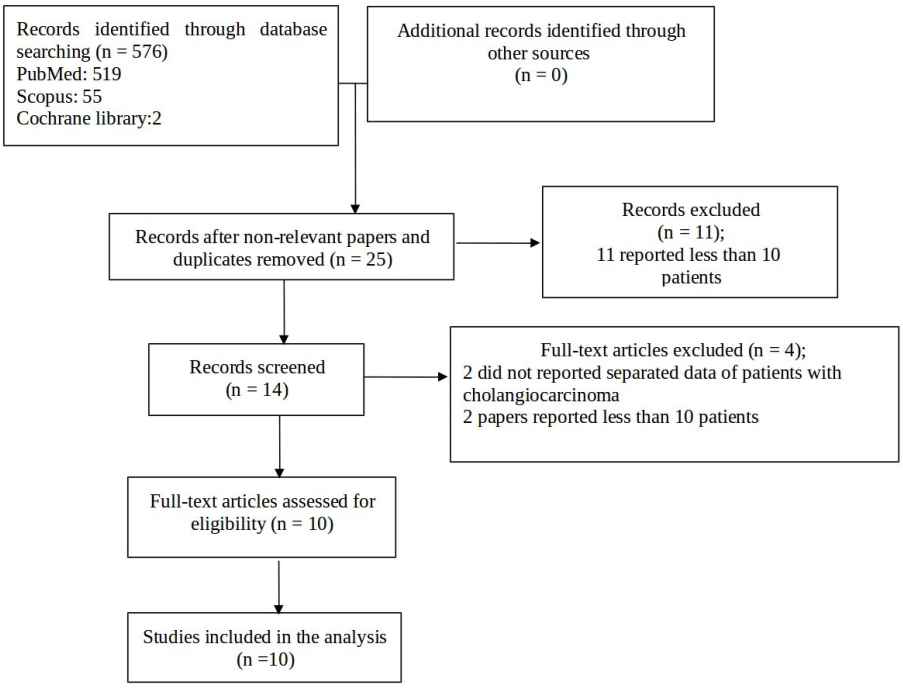
Clinically relevant late toxicity (≥G2) was reported in six studies.[19,20,22,24,26,27] The most frequent were duodenal complications (obstruction, ulceration, and hemorrhage ranging from 5.9 to 22.2%),[19,20,25–27] cholangitis (1.7–8.6%,)[20,22] and biliary stenosis (range: 1.7–8.3%).[22,24] Other less frequent toxicities are reported in Table 3. Only one case of fatal liver failure was

Table 3. Outcomes

Study	LC %	OS % 1 year	Median OS (months)	Median PFS (months)	Toxicity scale	Acute toxicity $G \geq 3$ %	Late toxicity $G \geq 3$ %
Barney et al. 2012[24]	Crude: 100	73.0	NR	NR	CTCAE *vs* 3.0	0.0	Biliary stenosis: 8.3 Liver failure: 8.3 (G5)
Ibarra et al. 2012[23]	NR	45.0	11	4.2	CTCAE *vs* 3.0	7.0	0.0
Jung et al. 2014[22]	1y: 85.0, 2y: 72.0	45.0 2y: 20.0	10	NR	CTCAE *vs* 4.0	0.0	Cholangitis: 8.6 Biliary stenosis: 1.7 Gastric perforation: 1.7 Gastric ulcer :1.7
Kopek et al. 2010[26]	1y: 84.0	NR	10.6	6.7	CTCAE *vs* 3.0/World Health Organization	Nausea: 3.7 Pain: 7.4 Liver enzyme: 55.5	Gastroduodenal ulceration: 22.2 Duodenal stenosis: 11.0
Mahadevan et al. 2015[20]	1y: 88.0	58.0, 2y: 31.0	17	10	NR	0.0	Duodenal ulceration:5.9 Cholangitis:1.7 Liver abscess:1.7
Polistina et al. 2011[25]	NR	80.0 2y: 80.0	[b]35.5	30.0	CTCAE *vs* 3.0	0.0	0.0
Sandler et al. 2016[19]	1y: 78.0 2y :47.0	59.0 2y: 33	15.7	16.8	CTCAE *vs* 4.0	Duodenal stenosis: 3.2	Duodenal stenosis: 6.4 Duodenal hemorrhage:10.3 Pain: 3.2
Shen et al. 2017[18]	Crude: 89.3	57.1 2y:32.1	15	11	CTCAE *vs* 4.0	0.0	0.0
Tse et al. 2008[27]	NR	58.0	15	NR	CTCAE *vs* 3.0	Liver Enzymes:20.0 Transient biliary obstruction: 20.0	Bowel obstruction: 10.0
Welling et al. 2014[21]	NR	83.0 (1)	NR	NR	SAEs	Cholangitis: 5.0 Dehydration: 7.0 Palmar-plantar erythrodysesthesia: 43.0 Diarrhea: 14.0 Wound infection post-surgery: 14.0	NR

CTCAE, common terminology criteria for adverse events; G, grade; NR, not reported; OS, overall survival; PFS, progression free survival; SAEs, Serious Adverse Events.
(1): in six transplanted patients.
[a]Median local progression free survival.
[b]calculated from time of diagnosis.

Figure 1. Flow chart study selection diagram.



reported in one patient despite compliance with dose/volume constraints.[24] According to the authors, this fatal event could have been related to subclinical liver damage due to previous CHT for breast cancer.[24]

Publication bias

The funnel plots were examined and none of them showed any asymmetry nor missing studies (figures not shown). The statistical analysis confirmed the absence of publication bias. However, caution regarding these results is warranted considering the small study numbers.

DISCUSSION

To the best of our knowledge, this is the first systematic review analyzing the role of SBRT in CC. Our study is limited by obvious reasons that include: retrospective design of most studies, small number of enrolled patients, few number and quality of the studies, and the high heterogeneity in terms of tumor characteristics, treatment aim, and prescribed dose. Certainly, the usefulness of a systematic review on such a limited and heterogeneous body of evidence can be discussed. However, we felt that in the absence of evidence from large prospective studies, this modality could still be useful to contribute to the knowledge in this field.

Figure 2. Forest plot of the 1 year overall survival reported in the analyzed studies.

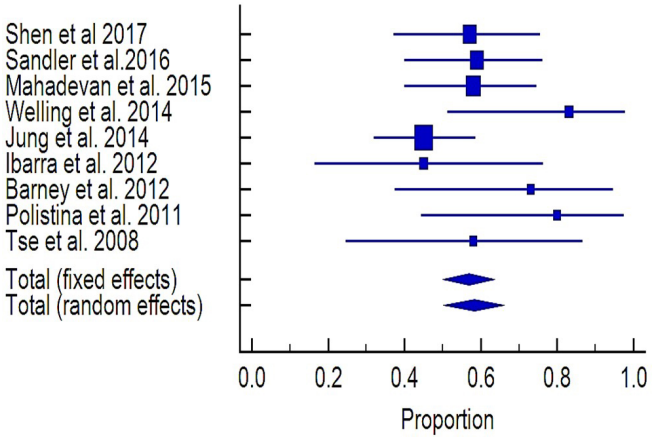


Figure 3. Forest plot of the 2 year overall survival reported in the analyzed studies.

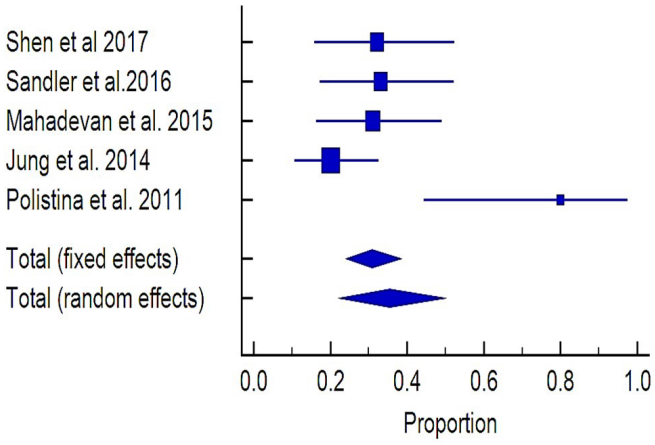
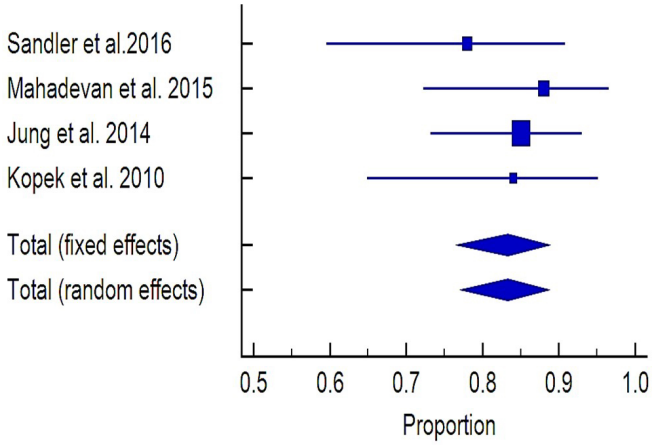


Figure 4. Forest plot of the 1 year local control reported in the analyzed studies.



Surgery with negative margins is considered to be the standard treatment in resectable CC. However, locally advanced/unresectable disease is the most common presentation of CC and Gemcitabine plus Cisplatin-based CHT is the standard treatment in these patients[27] with a median OS of 11.7 months.[28,29] Based on the ESMO guidelines,[27] the role of chemoradiation remains unclear in the treatment of locally advanced non-metastatic CC.

However, if we compare the results of CHT with the ones of chemoradiation, they seem very similar. In fact, in the systematic review of Bisello and colleagues, in the series based on chemoradiation ± brachytherapy boost, median PFS and OS were 7.5 months (range: 6.8–10.5 months) and 13 months (range: 9.6–13.5 months), respectively.[30]

More recently, SBRT has been tested in the treatment of advanced CC as an alternative to chemoradiation.[18–27] In fact, SBRT has several advantages like high biologically equivalent dose, short duration and therefore greater convenience for patients and departments, and easier integration with systemic therapies. Based on our analysis the results of SBRT in terms of survival are almost comparable with the ones of standard chemoradiation and CHT with 15.0 months median OS (range: 10.0–35.5 months). This result is particularly interesting considering that in the review of Bisello and colleagues,[30] the series including metastatic patients were excluded unlike in our analysis.

Comparing the results of studies enrolling only patients with intra hepatic CC,[18,23,27] we can observe that the highest 1 year OS rate (58%) was reported in the only prospective series included in this analysis.[27] In that trial, the SBRT dose prescription was based on the volume of the irradiated liver and the risk of liver toxicity was estimated by the Lyman-Kutcher-Burman normal tissue complication model. The study with the lowest 1 year OS rate (45%) was a retrospective multicenter analysis on heavily pre-treated patients (surgery, radiofrequency ablation, CHT).[23] This difference in terms of outcome might be related to the different study design, and to the different treatments performed before SBRT, the inclusion of metastatic patients, and the larger median PTV in the second study (172.0 cc *vs* 80.2 cc).

Another comparison can be done between two studies with similar characteristics in terms of CC type and site.[22,24] In fact, both studies included patients with intra/extra hepatic and primary/recurrent CC. In these two series, published by Jung and colleagues[22] and Barney and coworker,[24] 1 year OS was 45 and 73%, respectively. This difference could be related to the higher prescribed RT dose and to prescription of CHT in 40% of patients after SBRT in the study of Barney and colleagues.[24]

Surprisingly enough, the impact on survival of the inclusion of metastatic patients has been quite small. In fact, median 1 year survival was 51.1% (range: 45.0–58.0%) in series with M0-1 patients[18–22,24,25] and 59.0 (range: 45.0–83.0%) in series with only M0 patients,[23,27] respectively.

However, no clear impact of BED_{10Gy} on OS and LC was recorded in our analysis. In fact, median 1 year OS was 57.1% in series with BED_{10Gy} ≥100 Gy[18,22,24] and 58.5% in studies with BED_{10Gy} <100 Gy.[19,20,23,25] Similarly, 1 year LC, in patients with BED_{10Gy} ≥100 Gy and BED_{10Gy} <100 Gy was 84.0–85.0%[22,26] and 78.0–88.0%,[19,20] respectively. On the contrary, patients receiving CHT after SBRT showed higher 1 year OS rates (median: 73.0%; range: 58.0–80.0%)[20,24,25] compared to series without adjuvant CHT (median: 57.0%; range: 45.0–59.0%).[18,19,22,23,27]

Overall, treatment-related acute and late toxicities were acceptable even if with variable rates, and almost comparable with the ones reported after chemoradiation ± brachytherapy boost.[30] Only one treatment-related death was reported.[24] Unfortunately, it is impossible to correlate toxicity with dose and planning/delivery techniques due to the inhomogeneous and incomplete modalities of adverse events reporting.

This review demonstrates the minimal evidence available on this topic and highlights the need for high-quality studies in this area. Within this limit, the preliminary results in terms of OS seem not clearly different from the ones of standard chemoradiation. Moreover, SBRT seems reasonably effective in terms of LC with acceptable treatment-related toxicities. Again, considering the limitations of this analysis, its findings cannot justify changes in clinical practice or be considered as a recommendation. Therefore, SBRT can be considered as a therapeutic option at least in selected patients with CC, possibly combined with adjuvant CHT. Furthermore, from the excellent results recorded in patients undergoing neoadjuvant chemoradiation followed by orthotopic liver transplantation,[31] this latter treatment should always be considered in patients in whom this combined modality therapy is feasible.

Further studies are warranted in this field to better define the role of this technique in the advanced CC setting. These studies could have the following objectives: (i) comparison between CHT and CHT + SBRT; (ii) comparison between

chemoradiation and SBRT; (iii) evaluation of SBRT + CHT as neoadjuvant treatment aimed at tumor down-staging; (iv) combination of SBRT and CHT as bridge therapy in liver transplant candidates.

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