

Particle Therapy for Intrahepatic Cholangiocarcinoma: A Multicenter Prospective Registry Study, Systematic Review and Meta-Analysis

Masashi Mizumoto^a Kei Shibuya^b Kazuki Terashima^c Masao Murakami^d
Motohiro Murakami^a Yoshiyuki Shioyama^e Yoshiro Matsuo^c
Takashi Ogino^f Tatsuya Ohno^b Takahiro Waki^g Hiroyuki Ogino^h
Hiroyasu Tamamuraⁱ Norio Katoh^j Masaru Wakatsuki^k Tomoaki Okimoto^c
Motohisa Suzuki^d Takashi Saito^a Shingo Toyama^e Takayuki Hashimoto^l
Hisateru Ohba^k Shoji Kubo^m Kiyoshi Hasegawaⁿ Kazushi Maruo^o
Hideyuki Sakurai^a

^aDepartment of Radiation Oncology, University of Tsukuba, Tsukuba, Japan; ^bDepartment of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, Japan; ^cDepartment of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Japan; ^dDepartment of Radiation Oncology, Southern Tohoku Proton Therapy Center, Koriyama, Japan; ^eIon Beam Therapy Center, SAGA HIMAT Foundation, Tosu, Japan; ^fMedipolis Proton Therapy and Research Center, Ibusuki, Japan; ^gDepartment of Radiology, Tsuyama Chuo Hospital, Tsuyama, Japan; ^hDepartment of Radiation Oncology, Nagoya City University West Medical Center, Nagoya, Japan; ⁱProton Therapy Center, Fukui Prefectural Hospital, Fukui, Japan; ^jDepartment of Radiation Oncology, Hokkaido University Faculty of Medicine, Sapporo, Japan; ^kQST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan; ^lGlobal Center for Biomedical Science and Engineering, Hokkaido University Faculty of Medicine, Sapporo, Japan; ^mDepartment of Hepato-Biliary-Pancreatic Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; ⁿHepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; ^oDepartment of Biostatistics, Institute of Medicine, University of Tsukuba, Tsukuba, Japan

Highlights of the Study

- A prospective study and meta-analysis were performed to evaluate the efficacy and safety of particle therapy for intrahepatic cholangial carcinoma (ICC).
- Particle therapy resulted in superior overall survival and reduced local recurrence compared to SBRT and 3D-CRT.
- The incidence of grade 3 or higher late non-hematological toxicity was similar for the three modalities.
- Particle therapy may be indicated for unresectable ICC.

Keywords

Intrahepatic cholangiocarcinoma · Particle therapy · Radiotherapy · Meta-analysis · Systematic review

Abstract

Introduction: A prospective study was started in May 2016 to evaluate the efficacy and safety of particle therapy for intrahepatic cholangial carcinoma (ICC). To compare treatment modalities, we also conducted a meta-analysis of literature data and a systematic comparison using registry data. **Methods:** Patients who received particle therapy for ICC from May 2016 to June 2018 were registered. Nineteen manuscripts (4 particle therapy, 8 3D-CRT, 7 SBRT) were selected for the meta-analysis. **Results:** A total of 85 cases (proton beam therapy 59, carbon therapy 26) were registered. The median overall survival (OS) of the 85 patients was 22.1 months (95% CI: 12.9–31.3); the 1-, 2-, 3-, and 4-year OS rates were 70.9% (95% CI: 61.1–80.7%), 47.6% (36.8–58.4%), 37.7% (26.7–48.7%), and 22.7% (10.2–35.2%), respectively; and the 1-, 2-, 3-, and 4-year local recurrence rates were 8.2% (1.1–15.3%), 21.6% (9.3–33.9%), 33.4% (16.7–50.1%), and 33.4% (16.7–50.1%), respectively. In the meta-analysis and registry data, the 1-year OS for particle therapy, SBRT and 3D-CRT were 71.8% (95% CI: 64.6–77.8%), 59.2% (53.0–64.9%, $p = 0.0573$), and 47.2% (36.8–56.9%, $p = 0.0004$), respectively. The incidence of grade 3 or higher late non-hematological toxicity in the meta-analysis and registry data were 7.4–12% for particle therapy, 6.7–16.7% for SBRT, and 8.1–14.3% for 3D-CRT. **Conclusions:** Particle therapy achieved a good therapeutic effect for ICC, and a meta-analysis indicated that particle therapy is a better treatment modality than SBRT and 3D-CRT.

© 2024 The Author(s).

Published by S. Karger AG, Basel

Introduction

Intrahepatic cholangiocarcinoma (ICC) is common in Asia, and surgery and chemotherapy are the standard therapy [1, 2]. Surgery is the key to curative treatment and surgical indications are determined by the degree of tumor progression and postoperative residual liver function [3, 4]. The 5-year overall survival (OS) rates are 90–100% for stage I, 60–70% for stage II/III, and 20% for stage IV cases [4]. The outcome of surgical resection depends on the tumor size, lymph node metastasis, and portal vein tumor invasion, and the 5-year OS rate for patients with lymph node metastasis is thought to be 20%

or less [4, 5]. Unresectable ICC is treated with chemotherapy such as gemcitabine, cisplatin, and TS-1, but the therapeutic effect is poor and the median survival time (MST) is only about 1 year [6–8]. In a recent study of ICC with metastases, De et al. found that 82% of deaths with chemotherapy alone were caused by liver recurrence, whereas with radiotherapy this rate dropped to 47%, with distant metastasis becoming the leading cause of death [9]. These findings show the advantages of radiotherapy, including a lower rate of death caused by liver recurrence and longer survival.

Particle therapy is a suitable method for safe administration of high irradiation doses to tumors [10–12]. A prospective registration study of unresectable ICC without active metastases in Japan [13] found that the main cause of death was liver recurrence; however, more deaths were due to recurrence in the liver outside the irradiated area (24%) than local recurrence inside the irradiated area (15%). Distant metastasis (27%) and death from another disease (20%) were the second and third causes of death [13]. This suggests that local control by proton beam therapy (PBT) changes the cause of death from local recurrence to progression to another site (distant metastasis, intrahepatic recurrence outside the irradiated field), and this may contribute to prolongation of survival time. However, a systematic comparison among radiotherapy modalities for ICC has not been performed. To compare these modalities, we conducted a meta-analysis and a systematic comparison using a particle therapy prospective registry data.

Methods

Registry Data

The subjects were patients with ICC treated with PBT or carbon therapy from May 2016 to June 2018. The study was performed by the Intrahepatic Cholangiocarcinoma Working Group in the Particle Beam Therapy Committee and Subcommittee of the Japanese Society for Radiation Oncology (JASTRO), and the results for PBT have been reported elsewhere [13]. A total of 85 cases were included, including 59 treated with PBT and 26 that received carbon therapy. The characteristics of the patients who received carbon therapy are shown in Table 1. At final follow-up, 30 patients were alive and 55 had died. The median follow-up period for survivors was 33.6 months (1–55 months). The median OS of the 85 patients was 22.1 months (95% CI: 12.9–31.3), with 1-, 2-, 3-, and 4-year OS rates of 70.9%

Table 1. Characteristics of patients and tumors treated by carbon therapy ($n = 26$)

Characteristics	N	%
Age (years)	34–91	75 (median)
Gender		
Male	15	57.7
Female	11	42.3
Surgical indication		
Operable	5	19.2
Inoperable	21	80.8
ECOG performance status		
0	20	76.9
1	3	11.5
2	3	11.5
History of hepatitis		
Yes	9	34.6
No	17	65.4
Child-Pugh class		
A	24	92.3
B	2	7.7
Tumor size, mm	10–109	30 (median)
<30	12	46.2
30–49	7	26.9
50–99	4	15.4
≥100	3	11.5
Portal vein tumor thrombus		
Vp 0–2	24	92.3
Vp 3–4	2	7.7
Prior treatment		
Yes	6	23.1
No	20	76.9
Prior radiotherapy		
Yes	1	3.8
No	25	96.2
Clinical stage		
I	10	38.5
II	13	50.0
III	1	3.8
IV	2	7.7

ECOG, Eastern Cooperative Oncology Group.

(95% CI: 61.1–80.7%), 47.6% (36.8–58.4%), 37.7% (26.7–48.7%), and 22.7% (10.2–35.2%), respectively. There was local recurrence in 13 cases, and the 1-, 2-, 3-, and 4-year local recurrence rates of 8.2% (1.1–15.3%), 21.6% (9.3–33.9%), 33.4% (16.7–50.1%), and 33.4% (16.7–50.1%), respectively. OS and local recurrence rates are shown in Figure 1. These outcomes were used in the meta-analysis.

Meta-Analysis

A review was conducted in compliance with the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and recommendations [14]. Only English language articles were included. All retrieved articles were screened by two reviewers. The inclusion criteria were (1) clinically diagnosed primary ICC, (2) received radical radiotherapy (3D-CRT, SBRT or particle therapy), (3) surgery not used concurrently (surgery after recurrence was acceptable), (4) median survival or survival rate with radiotherapy included in the manuscript, and (5) at least 10 or more treatment outcomes specified. Studies published from 2000 to 2016 that used ICC clinical practice guidelines and satisfied these five criteria were selected. More recent studies from 2016 to 2020 that also met the criteria were identified from 308 articles retrieved in a PubMed search using the keywords “Radiotherapy” AND “Intrahepatic cholangiocarcinoma” (Fig. 2).

From the 308 articles from 2016 to 2020, 28 that described outcomes of radiotherapy were selected based on the abstract. Further reading of the text identified 10 of the 28 articles in which the 1- to 3-year OS or MST were specified in the manuscript. Finally, with inclusion of the pre-2016 studies, a total of 19 studies (4 particle therapy, 8 3D-CRT, 7 SBRT) were selected after excluding those with significant bias in patient background and overlapping publication periods from the same center. Table 2 shows all the selected studies [15–32]. Data obtained from each study included the authors, year of publication, country, study design, number of patients, number of deaths, follow-up period, MST, 1-, 2-, and 3-year OS rates, tumor size, number of portal vein tumor thrombosis cases, number of metastases outside the liver, and irradiation method (particle therapy, SBRT, 3D-CRT). If MST and OS were not written in the text, these outcomes were extracted from figures.

Statistical Analysis

Random-effects meta-analyses of 1-, 2-, and 3-year OS rates and MST were performed for each modality, and forest plots were drawn. For studies with missing accuracy information, missing values were imputed using information on the number of cases, risk set size at each year, and mean dropout rate. Heterogeneity in each meta-analysis was evaluated by I-square statistics. Random-effects meta-regressions with modality as an explanatory variable were also performed for each outcome to compare among the modalities. All analyses were performed using R software (R Core Team, Vienna, Austria) and its Meta package [33].

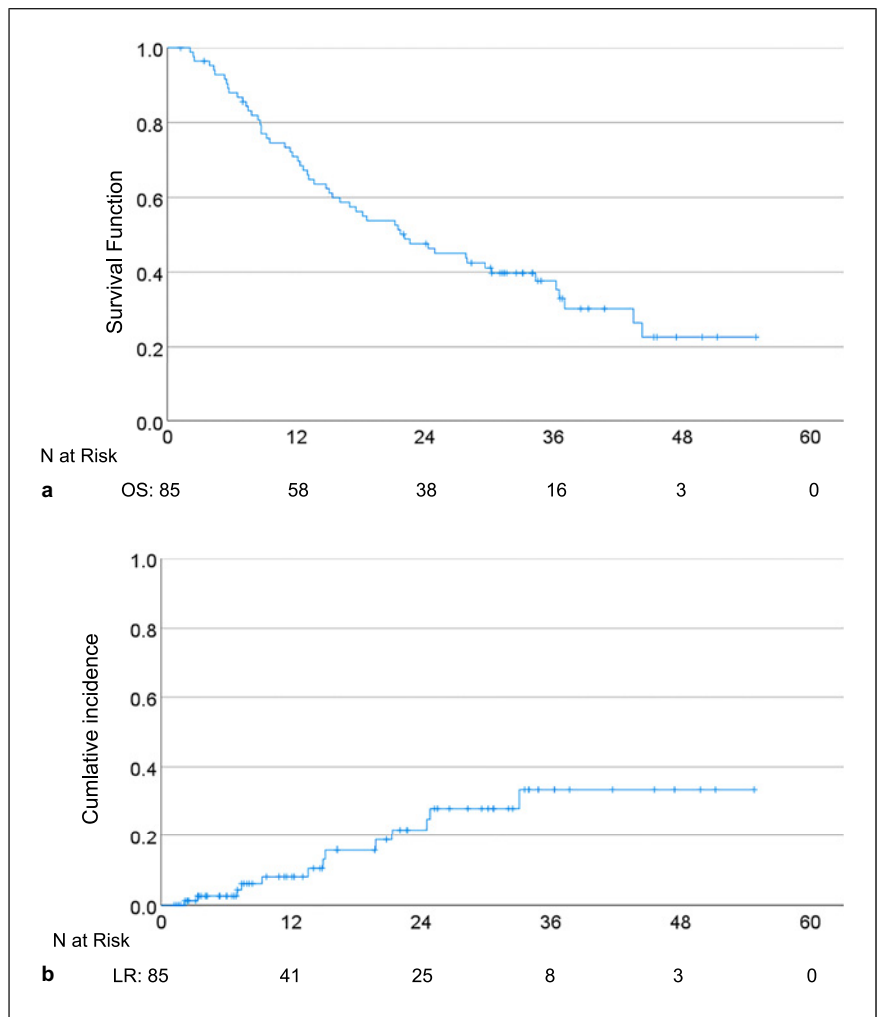


Fig. 1. a Overall survival rate for all patients.
b Local recurrence rate for all patients.

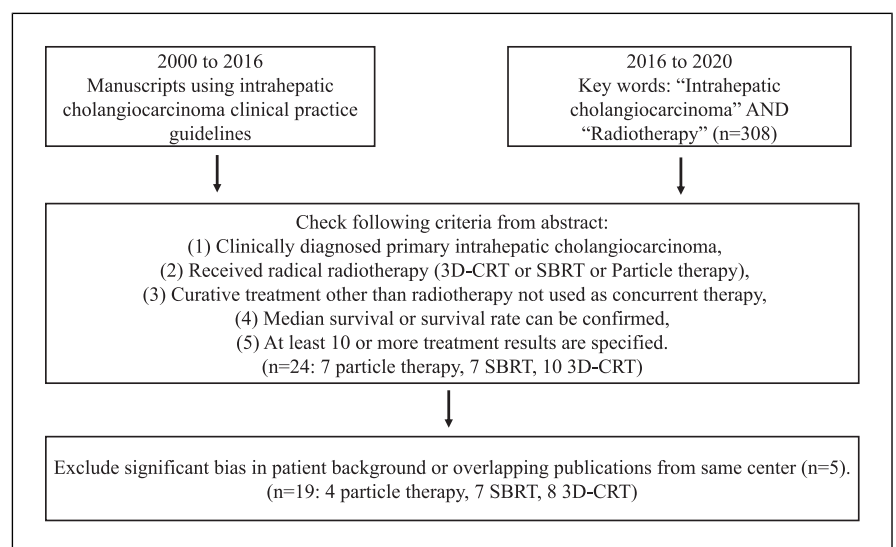


Fig. 2. Manuscript selection process.

Table 2. List of selected manuscripts

Author	Year	Modality	Study	<i>n</i>	Size, mm	1yOS, %	2yOS, %	3yOS, %	MST, month
Parazen	2020	Proton	P	25	55	81.8	35		20.1
Shimizu et al. [16]	2019	Proton	R	25	44	66.3	52.4	42	25
Kasuya et al. [17]	2019	Carbon	R	27	43	77.8	53.4	38	23.8
Hong et al. [18]	2016	Proton	P	39	60	69.7	46.5	36	22.5
Registry	2021	Particle	P	85	48	70.9	47.6	37.7	22.1
Brunner et al. [19]	2019	SBRT	R	64	44	61	34	20	15
Sebastian et al. [20]	2019	SBRT	R	27	45	85	55	52	48
Shen et al. [21]	2017	SBRT	R	28		57.1	32.1	7	15
Gkika et al. [22]	2017	SBRT	R	17	49	57	25		14
Weiner et al. [24]	2016	SBRT	P	12	50	51			13.2
Jung et al. [23]	2014	SBRT	R	33		45	20	18	10
Tse et al. [25]	2008	SBRT	R	10		58			15
Sebastian et al. [20]	2019	3DCRT	R	54	44	55	31	15	14
Chang ¹ et al. [26]	2018	3DCRT	DB	211		43	23	11	10.3
Chang ² et al. [26]	2018	3DCRT	DB	211		22	10	4	6.7
Verma et al. [27]	2018	3DCRT	DB	666		62	30	17	13.6
Shinohara et al. [28]	2009	3DCRT	DB	396					7
Zeng et al. [29]	2006	3DCRT	R	38		50.1	11.8	5	12
Crane et al. [30]	2002	3DCRT	R	52		44	13		10
Shinch et al. [31]	2000	3DCRT	R	30		56.9	0		13
Dawson et al. [32]	2000	3DCRT	R	27	100	48	30		11

P, prospective study; R, retrospective study; Chang¹, concurrent chemotherapy; Chang², non-concurrent chemotherapy; DB, treatment results from database.

Results

Meta-analysis was first performed using all selected studies and registry data. The 1-, 2- and 3-year OS rates for particle therapy, SBRT and 3D-CRT were (1-year) 71.8% (95% CI: 64.6–77.8%), 59.2% (53.0–64.9%, $p = 0.0573$), and 47.2% (36.8–56.9%, $p = 0.0004$); (2-year) 47.5% (39.6–54.9%), 32.6% (23.3–42.3%, $p = 0.1532$), and 16.6% (8.4–27.2%, $p = 0.0002$); and (3-year) 38.3% (28.8–47.6%), 20.5% (8.2–36.7%, $p = 0.0605$), and 10.3% (5.2–17.3%, $p = 0.0001$), respectively. Forest plots for each modality for 1-, 2-, and 3-year OS rates are shown in Figures 3–5. The MSTs of particle therapy, SBRT and 3D-CRT were 22.7 (95% CI: 17.6–29.2), 15.9 (11.3–22.3, $p = 0.1082$), and 10.2 (8.3–12.5, $p = 0.0001$) months, respectively. Forest plots for each modality for MST are shown in Figure 6.

Meta-regressions (Table 3) indicated significant associations of SBRT and 3D-CRT with a poor 1-year OS rate and of 3D-CRT with a poor 2-year OS rate. 3D-CRT also showed a tendency for associations with a poor 3-year OS rate and MST. In I-square statistics, 3D-CRT had high heterogeneity among studies. Meta-regressions including tumor size were also performed. The median tumor sizes were 43–60 mm for particle therapy, 44–100 mm for 3D-CRT, and 44–50 mm for SBRT. To the extent that information was available in the articles, the total doses and fraction (fr) sizes were 67.5 Gy(RBE) in 15 fr to 76 Gy(RBE) in 20 fr for particle therapy; 36 Gy in 6 fr to 55 Gy in 5 fr for SBRT; and 50 Gy in 25 fr to 60 Gy in 30 fr for 3D-CRT. The irradiation dose was adjusted to give the biological effective dose (BED₁₀): particle therapy (80.5–104.9 Gy[BED₁₀]; median 96.6), SBRT (57.6–115.5 Gy[BED₁₀]; median 85.5), and 3D-CRT

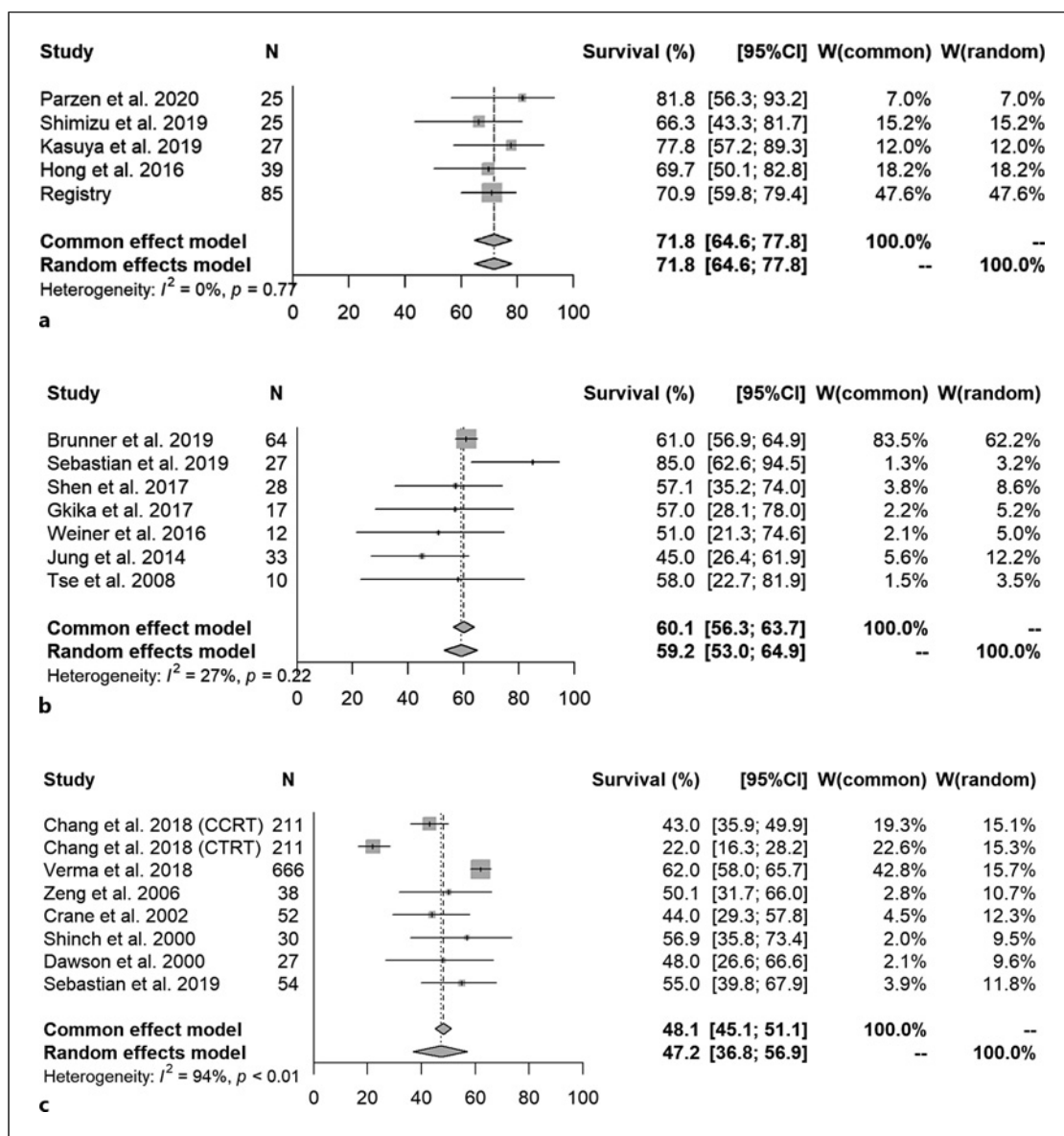


Fig. 3. Forest plot for each modality for 1-year overall survival rate. **a** 1-year overall survival rate of all selected manuscript (Particle therapy). **b** 1-year overall survival rate of all selected manuscript (SBRT). **c** 1-year overall survival rate of all selected manuscript (3DCRT).

(59.5–72.0 Gy[BED₁₀]; median 63.5). The recurrence pattern was not described in detail in many studies, but the rates of first recurrence sites outside the irradiation field were 59–79% (median 73%) for particle therapy, 79–85% (median 82%) for SBRT, and 18–54% (median 26%) for 3DCRT. The proportion of patients with poor liver function (Child-Pugh class B or C) ranged from 4 to 20% (median 10.3%) for particle therapy, 0–28.6% (median 12%) for SBRT and was not evaluable for 3DCRT. The incidences of grade 3 or higher late non-

hematological toxicity were 7.4–12% for particle therapy, 6.7–16.7% for SBRT, and 8.1–14.3% for 3D-CRT.

Discussion

The tolerable dose in cases with normal liver function is 20–30 Gy, and <10 Gy for patients with poor liver function due to hepatitis [34–36]. In 3D-CRT,

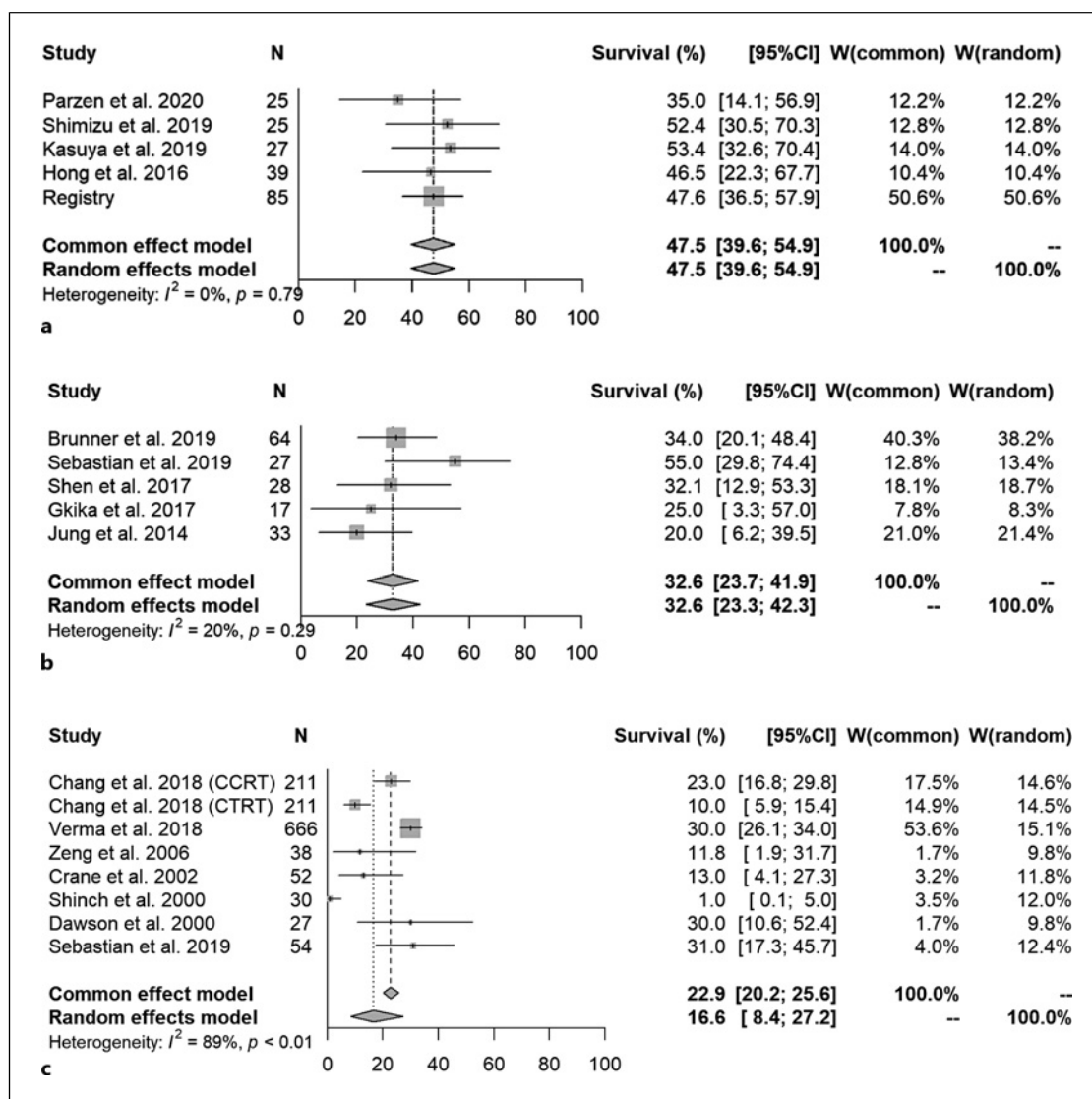


Fig. 4. Forest plot for each modality for 2-year overall survival rate. **a** 2-year overall survival rate of all selected manuscript (Particle therapy). **b** 2-year overall survival rate of all selected manuscript (SBRT). **c** 2-year overall survival rate of all selected manuscript (3DCRT).

the standard irradiation dose is 50 Gy based on the tolerable dose of the peripheral gastrointestinal tract, spinal cord and normal liver [26–32]. In recent years, advances in irradiation technology have made it possible to administer higher doses to tumors safely using SBRT and particle therapy [15–25]. In fact, in the studies used in this meta-analysis, the dose increased from 3D-CRT (59.5–72 Gy[BED₁₀]) to SBRT (57.6–115.5 Gy[BED₁₀]) and particle therapy (80.5–104.9 Gy[BED₁₀]). Adverse events are difficult to analyze given the different conditions, but the incidence of non-hematological late adverse events of

Grade 3 or higher in the selected studies was about 10% [15–32], with no significant difference in the frequency or type of late adverse events among the irradiation methods. This result shows that particle therapy can be used to administer higher doses with lower or similar adverse events to those with SBRT in clinical practice. In comparison with the articles included in this meta-analysis, most recurrence types in 3DCRT were in-field recurrences, whereas in SBRT and particle therapy, out-of-field recurrences accounted for more than 70% of recurrences. These results suggest that high doses of SBRT and particle

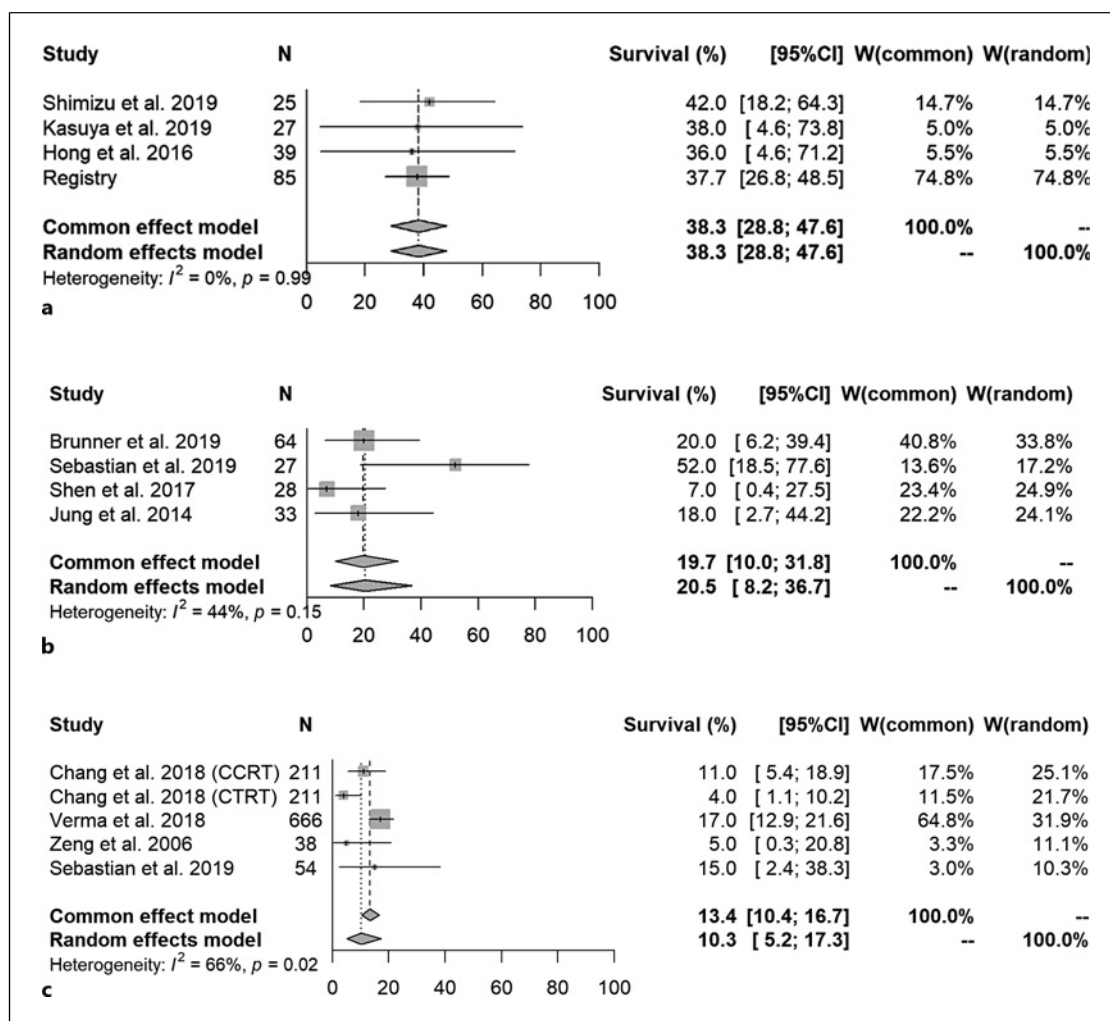


Fig. 5. Forest plot for each modality for 3-year overall survival rate. **a** 3-year overall survival rate of all selected manuscript (Particle therapy). **b** 3-year overall survival rate of all selected manuscript (SBRT). **c** 3-year overall survival rate of all selected manuscript (3DCRT).

therapy for ICC may reduce mortality due to local recurrence and contribute to prolonged survival. Detailed comparisons of patient backgrounds are difficult to make, but about 90% of the cases in papers that described liver function were Child-Pugh A. Multivariate analysis including tumor size and treatment modalities showed poor survival for 3DCRT and similar or slightly better results for particle therapy than for SBRT. These results suggest that high doses of particle therapy and SBRT to the primary tumor are effective for improving survival. A comparison of particle therapy and SBRT showed no significant difference other than 1-year OS rate, but particle therapy gave better overall treatment outcomes.

Similarly to ICC, hepatocellular carcinoma (HCC) requires high-dose irradiation of the liver. In a systematic review of radiotherapy for HCC, particle therapy and SBRT had almost the same treatment results, while 3D-CRT with TACE had poorer outcomes [37]. Both SBRT and particle therapy are expected to achieve high local control for small HCCs of 3–4 cm or less [38, 39]. All articles included in the current meta-analysis had a median tumor size of 4 cm or greater, and the significant difference in 1-year OS between particle therapy and SBRT in the meta-analysis is probably due to the larger tumor size. Thus, for ICC, in which lesions often exceed 4 cm, particle therapy is suitable for safe irradiation of a large tumor. Given that most recurrences in particle

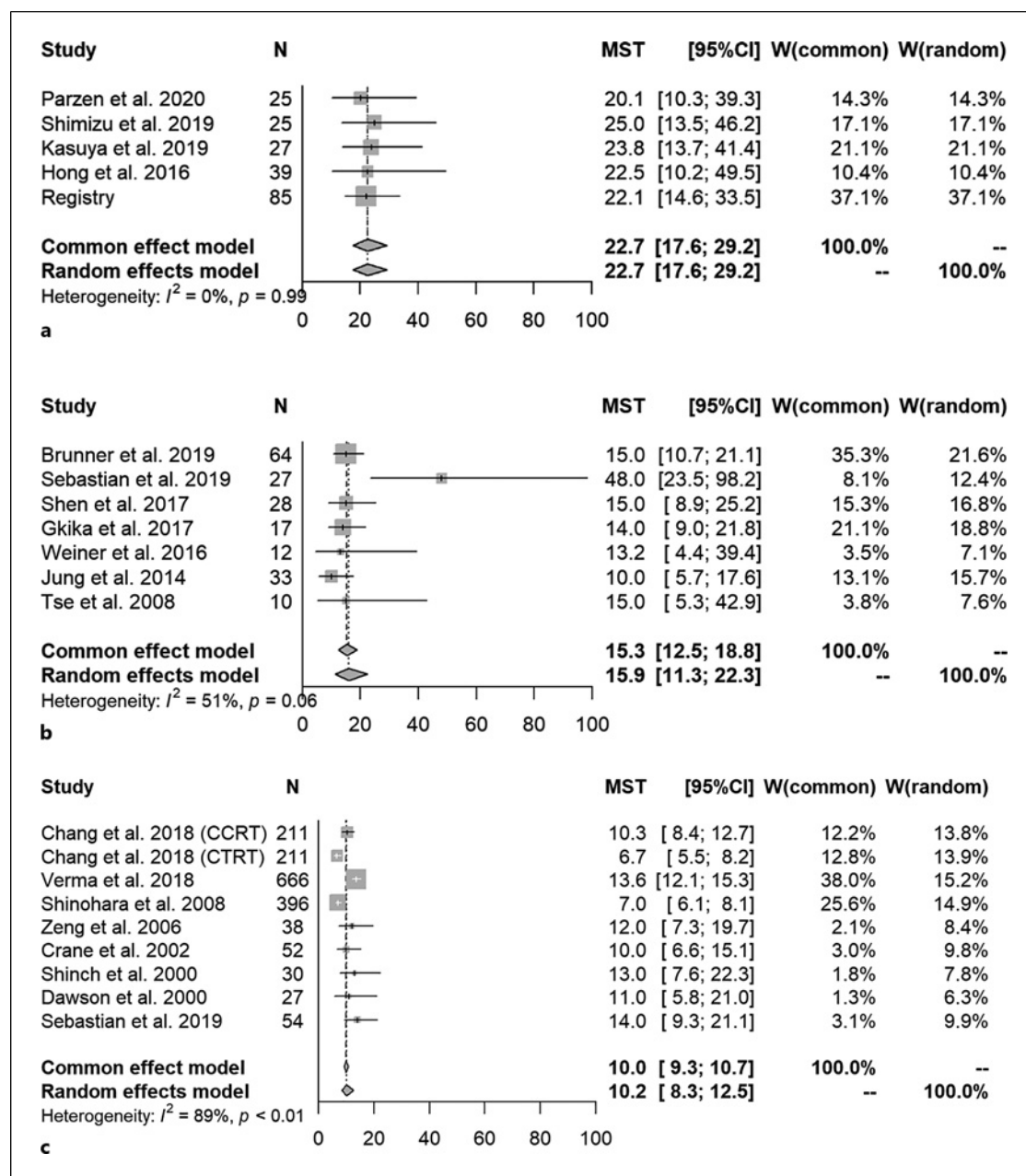


Fig. 6. Forest plot for each modality for MST. **a** MST of all selected manuscript (Particle therapy). **b** MST of all selected manuscript (SBRT). **c** MST of all selected manuscript (3DCRT).

therapy and SBRT cases occur outside the irradiated area, chemotherapy, which is the standard treatment for unresectable cases of ICC and distant metastases, is essential.

Chemotherapy is the standard treatment, and GEM, CDDP, and TS-1 are used in combination [40–43]. Using these treatments, the MST of chemotherapy for

unresectable ICC is about 12–15 months and the main cause of death is exacerbation of a local lesion, whereas with particle therapy, the main cause of death is distant metastasis [9, 13]. Since ICC is a rare disease, it is difficult to conduct randomized trials to verify the optimal combination. The results for particle therapy suggest that it is indicated for unresectable ICC, where

Table 3. Meta-regressions of potential predictive factors for 1- to 3-year OS and MST

Factors	Estimate	SE	zval	Pval	ci.lb	ci.ub
1-year OS						
3DCRT	0.5959	0.2847	2.0936	0.0363	0.0380	1.1539
SBRT	0.3761	0.1641	2.2918	0.0219	0.0545	0.6977
Tumor size	−0.0039	0.0099	−0.3979	0.6907	−0.0233	0.0154
2-year OS						
3DCRT	0.5181	0.2529	2.0487	0.0405	0.0224	1.0138
SBRT	0.2936	0.2024	1.4504	0.1469	−0.1032	0.6904
Tumor size	0.0039	0.0099	0.6934	0.6934	−0.0155	0.0232
3-year OS						
3DCRT	0.6963	0.4000	1.7407	0.0817	−0.0877	1.4803
SBRT	0.3052	0.3086	0.9892	0.3226	−0.2996	0.9100
Tumor size	0.0042	0.0388	0.1084	0.9137	−0.0718	0.0802
MST						
3DCRT	−0.5283	0.3157	−1.6733	0.0943	−1.1471	0.0905
SBRT	−0.2618	0.2155	−1.2149	0.2244	−0.6841	0.1605
Tumor size	0.0021	0.0115	0.1876	0.8512	0.0203	0.0246

OS, overall survival; MST, median survival time.

local lesions are expected to be the main cause of death, regardless of distant metastases. At present, particle therapy for ICC is performed for about 4–7 weeks. Given that the main cause of death after radiotherapy is distant metastasis, concurrent chemotherapy or an early transition to systemic chemotherapy may be beneficial for shortening the irradiation period [9, 13]. However, a future study is needed to establish the optimal dose fraction and total dose of particle therapy in combination with systemic therapy for ICC.

Conclusion

Particle therapy achieved a good therapeutic effect for ICC, and a meta-analysis indicated that particle therapy is a better treatment modality than SBRT and 3DCRT. The next task is to determine a suitable indication and to consider the optimal combination of particle therapy with systemic therapy.

Statement of Ethics

The study protocol was reviewed and approved by the Ethical Review Board for Life Science and Medical Research, Hokkaido University Hospital (Approval No.: 016-0106). Written informed consent was obtained from all participants in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by Hokkaido University (Functional Enhancement Promotion funding from the Ministry of Education, Culture, Sports, Science and Technology) and AMED under Grant No. JP16lm0103004. The sponsors had no role in the preparation of data, the decision to publish the manuscript, or the writing of the manuscript.

Author Contributions

Conception/design: MaMi, K.S., S.K., K.H., and H.S. Provision of study materials or patients: K.T., MaMu, MoMu, Y.S., Y.M., TaOg, TaOh, T.W., H.O., H.T., N.K., M.W., T.O., M.S., T.S., and S.T. Collection and assembly of data: T.H., H.O. Data analysis and interpretation: MaMi, K.M., and K.S. Manuscript writing: MaMi and K.S. Final approval of manuscript: H.S. All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- Lee TY, Lin JT, Kuo KN, Wu MS, Ho HJ, Chen TT, et al. A nationwide population-based study shows increasing incidence of cholangiocarcinoma. *Hepatol Int*. 2013;7(1):226–32. <https://doi.org/10.1007/s12072-012-9369-0>
- Kim BW, Oh CM, Choi HY, Park JW, Cho H, Ki M. Incidence and overall survival of biliary tract cancers in South Korea from 2006 to 2015: using the national health information database. *Gut Liver*. 2019;13(1):104–13. <https://doi.org/10.5009/gnl18105>
- <https://www.nccn.org/patients/guidelines/content/PDF/gallandbile-hp-patient.pdf>
- Sakamoto Y, Kokudo N, Matsuyama Y, Sakamoto M, Izumi N, Kadoya M, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer*. 2016;122(1):61–70. <https://doi.org/10.1002/cncr.29686>
- Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, et al. Report of the 20th Nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res*. 2020;50(1):15–46. <https://doi.org/10.1111/hepr.13438>
- Valle J, Wasan H, Palmer DH, Cunningham D, Anthony A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273–81. <https://doi.org/10.1056/NEJMoa0908721>
- Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol*. 2014;25(2):391–8. <https://doi.org/10.1093/annonc/mdt540>
- Morizane C, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. *Ann Oncol*. 2019;30(12):1950–8. <https://doi.org/10.1093/annonc/mdz402>
- De B, Upadhyay R, Liao K, Kumala T, Shi C, Dodoo G, et al. Definitive liver radiotherapy for intrahepatic cholangiocarcinoma with extrahepatic metastases. *Liver Cancer*. 2023;12(3):198–208. <https://doi.org/10.1159/000530134>
- Mizumoto M, Fuji H, Miyachi M, Soejima T, Yamamoto T, Aibe N, et al. Proton beam therapy for children and adolescents and young adults (AYAs): JASTRO and JSPHO Guidelines. *Cancer Treat Rev*. 2021;98:102209. <https://doi.org/10.1016/j.ctrv.2021.102209>
- Demizu Y, Mizumoto M, Onoe T, Nakamura N, Kikuchi Y, Shibata T, et al. Proton beam therapy for bone sarcomas of the skull base and spine: a retrospective nationwide multicenter study in Japan. *Cancer Sci*. 2017;108(5):972–7. <https://doi.org/10.1111/cas.13192>
- Oshiro Y, Mizumoto M, Okumura T, Hashimoto T, Fukumitsu N, Ohkawa A, et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol*. 2012;7(2):370–5. <https://doi.org/10.1097/JTO.0b013e31823c485f>
- Mizumoto M, Terashima K, Makishima H, Suzuki M, Ogino T, Waki T, et al. Proton beam therapy for intrahepatic cholangiocarcinoma: a multicenter prospective registry study in Japan. *Liver Cancer*. 2024;13(2):161–8. <https://doi.org/10.1159/000531376>
- <http://prisma-statement.org/prismastatement/checklist.aspx?AspxAutoDetectCookieSupport=1>
- Parzen JS, Hartsell W, Chang J, Apisarnthanarax S, Molitoris J, Durci M, et al. Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: multi-institutional prospective results from the Proton Collaborative Group. *Radiat Oncol*. 2020;15(1):255. <https://doi.org/10.1186/s13014-020-01703-3>
- Shimizu S, Okumura T, Oshiro Y, Fukumitsu N, Fukuda K, Ishige K, et al. Clinical outcomes of previously untreated patients with unresectable intrahepatic cholangiocarcinoma following proton beam therapy. *Radiat Oncol*. 2019;14(1):241. <https://doi.org/10.1186/s13014-019-1451-5>
- Kasuya G, Terashima K, Shibuya K, Toyama S, Ebner DK, Tsuji H, et al. Carbon-ion radiotherapy for cholangiocarcinoma: a multi-institutional study by and the Japan carbon-ion radiation oncology study group (J-CROS). *Oncotarget*. 2019;10(43):4369–79. <https://doi.org/10.18632/oncotarget.27028>
- Hong TS, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, Blaszkowsky LS, et al. Multi-institutional phase ii study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34(5):460–8. <https://doi.org/10.1200/JCO.2015.64.2710>
- Brunner TB, Blanck O, Lewitzki V, Abbasi-Senger N, Momm F, Riesterer O, et al. Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *Radiation Oncol*. 2019;132:42–7. <https://doi.org/10.1016/j.radonc.2018.11.015>
- Sebastian NT, Tan Y, Miller ED, Williams TM, Alexandra Diaz D. Stereotactic body radiation therapy is associated with improved overall survival compared to chemoradiation or radioembolization in the treatment of unresectable intrahepatic cholangiocarcinoma. *Clin Transl Radiat Oncol*. 2019;19:66–71. <https://doi.org/10.1016/j.ctro.2019.07.007>
- Shen ZT, Zhou H, Li AM, Li B, Shen JS, Zhu XX. Clinical outcomes and prognostic factors of stereotactic body radiation therapy for intrahepatic cholangiocarcinoma. *Oncotarget*. 2017;8(55):93541–50. <https://doi.org/10.18632/oncotarget.19972>
- Gkika E, Hallauer L, Kirste S, Adebahr S, Bartl N, Neeff HP, et al. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *BMC Cancer*. 2017;17(1):781. <https://doi.org/10.1186/s12885-017-3788-1>
- Jung DH, Kim MS, Cho CK, Yoo HJ, Jang WI, Seo YS, et al. Outcomes of stereotactic body radiotherapy for unresectable primary or recurrent cholangiocarcinoma. *Radiat Oncol J*. 2014;32(3):163–9. <https://doi.org/10.3857/roj.2014.32.3.163>
- Weiner AA, Olsen J, Ma D, Dyk P, DeWees T, Myerson RJ, et al. Stereotactic body radiotherapy for primary hepatic malignancies - report of a phase I/II institutional study. *Radiation Oncol*. 2016;121(1):79–85. <https://doi.org/10.1016/j.radonc.2016.07.020>
- Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2008;26(4):657–64. <https://doi.org/10.1200/JCO.2007.14.3529>
- Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM, Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. *Radiation Oncol*. 2018;129(2):284–92. <https://doi.org/10.1016/j.radonc.2018.09.010>
- Verma V, Kusi Appiah A, Lautenschlaeger T, Adeberg S, Simone CB 2nd, Lin C. Chemoradiotherapy versus chemotherapy alone for unresected intrahepatic cholangiocarcinoma: practice patterns and outcomes from the national cancer data base. *J Gastrointest Oncol*. 2018;9(3):527–35. <https://doi.org/10.21037/jgo.2018.01.15>
- Shinohara ET, Mitra N, Guo M, Metz JM. Radiotherapy is associated with improved survival in adjuvant and palliative treatment of extrahepatic cholangiocarcinomas. *Int J Radiat Oncol Biol Phys*. 2009;74(4):1191–8. <https://doi.org/10.1016/j.ijrobp.2008.09.017>
- Zeng ZC, Tang ZY, Fan J, Zhou J, Qin LX, Ye SL, et al. Consideration of the role of radiotherapy for unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 75 patients. *Cancer J*. 2006;12(2):113–22.

- 30 Crane CH, Macdonald KO, Vauthey JN, Yehuda P, Brown T, Curley S, et al. Limitations of conventional doses of chemotherapy for unresectable biliary cancer. *Int J Radiat Oncol Biol Phys.* 2002;53(4):969–74. [https://doi.org/10.1016/s0360-3016\(02\)02845-6](https://doi.org/10.1016/s0360-3016(02)02845-6)
- 31 Shinci H, Takao S, Nishida H, Aikou T. Length and quality of survival following external beam radiotherapy combined with expandable metallic stent for unresectable hilar cholangiocarcinoma. *J Surg Oncol.* 2000;75(2):89–94. [https://doi.org/10.1002/1096-9098\(200010\)75:2<89::aid-jsoc3>3.0.co;2-v](https://doi.org/10.1002/1096-9098(200010)75:2<89::aid-jsoc3>3.0.co;2-v)
- 32 Dawson LA, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. *J Clin Oncol.* 2000;18(11):2210–8. <https://doi.org/10.1200/JCO.2000.18.11.2210>
- 33 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Health.* 2019;22(4):153–60. <https://doi.org/10.1136/ebmental-2019-300117>
- 34 Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. *Int J Radiat Oncol Biol Phys.* 2002;53(4):810–21. [https://doi.org/10.1016/s0360-3016\(02\)02846-8](https://doi.org/10.1016/s0360-3016(02)02846-8)
- 35 Kim TH, Kim DY, Park JW, Kim SH, Choi JI, Kim HB, et al. Dose-volumetric parameters predicting radiation-induced hepatic toxicity in unresectable hepatocellular carcinoma patients treated with three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;67(1):225–31. <https://doi.org/10.1016/j.ijrobp.2006.08.015>
- 36 Liang SX, Huang XB, Zhu XD, Zhang WD, Cai L, Huang HZ, et al. Dosimetric predictor identification for radiation-induced liver disease after hypofractionated conformal radiotherapy for primary liver carcinoma patients with Child-Pugh Grade A cirrhosis. *Radiother Oncol.* 2011;98(2):265–9. <https://doi.org/10.1016/j.radonc.2010.10.014>
- 37 Qi WX, Fu S, Zhang Q, Guo XM. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol.* 2015;114(3):289–95. <https://doi.org/10.1016/j.radonc.2014.11.033>
- 38 Takeda A, Sanuki N, Tsurugai Y, Iwabuchi S, Matsunaga K, Ebinuma H, et al. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. *Cancer.* 2016;122(13):2041–9. <https://doi.org/10.1002/cncr.30008>
- 39 Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol.* 2016;34(5):452–9. <https://doi.org/10.1200/JCO.2015.61.4925>
- 40 Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer.* 2010;103(4):469–74. <https://doi.org/10.1038/sj.bjc.6605779>
- 41 Ioka T, Kanai M, Kobayashi S, Sakai D, Eguchi H, Baba H, et al. Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). *J Hepatobiliary Pancreat Sci.* 2023;30(1):102–10. <https://doi.org/10.1002/jhbp.1219>
- 42 Valle JW, Furuse J, Jital M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol.* 2014;25(2):391–8. <https://doi.org/10.1093/annonc/mdt540>
- 43 Morizane C, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. *Ann Oncol.* 2019;30(12):1950–8. <https://doi.org/10.1093/annonc/mdz402>