Stereotactic body radiation therapy is associated with improved overall survival compared to chemoradiation or radioembolization in the treatment of unresectable intrahepatic cholangiocarcinoma

Nikhil T. Sebastian a, Yubo Tan b, Eric D. Miller a, Terence M. Williams a, Dayssy Alexandra Diaz a,*

a Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, 460 W. 10th Ave, Columbus, OH 43210, USA
b Department of Biomedical Informatics, The Ohio State University College of Medicine, 320 Lincoln Tower, 1800 Cannon Drive, Columbus, OH 43210, USA

A R T I C L E   I N F O

Article history:
Received 9 May 2019
Revised 22 July 2019
Accepted 24 July 2019
Available online 26 July 2019

Keywords:
Intrahepatic cholangiocarcinoma
Stereotactic body radiation therapy
Chemoradiation
Transarterial radioembolization

A B S T R A C T

Background: Intrahepatic cholangiocarcinoma (ICC) is a highly lethal malignancy. For patients with locally advanced, unresectable disease, numerous liver-directed therapy options exist, including chemoradiation (CRT), stereotactic body radiation therapy (SBRT), and transarterial radioembolization (TARE). There is no randomized data to inform clinicians regarding the optimal treatment modality.

Method: We used the National Cancer Database (NCDB) to study the overall survival (OS) of patients with ICC treated with CRT, SBRT, and TARE. We used Cox proportional hazards modeling and inverse probability of treatment weighting (IPTW) to account for confounding variables.

Results: We identified 170 patients with unresected ICC treated with SBRT (n = 37), CRT (n = 61), or TARE (n = 72). SBRT was associated with higher OS compared to CRT (hazard ratio [HR] = 0.37; 95% confidence interval [CI] 0.20–0.68; p = 0.001) and TARE (HR = 0.40; 95% CI 0.22–0.74; p = 0.003). On multivariable analysis, SBRT remained associated with higher OS compared to CRT (HR = 0.44; 95% CI 0.21–0.91; p = 0.028) and TARE (HR = 0.42; 95% CI 0.21–0.84; p = 0.014). After IPTW (Bonferroni-adjusted significance threshold, α = 0.017), SBRT again had a statistically significant association with higher OS compared to CRT (HR = 0.22; 95% CI 0.11–0.44; p < 0.0001) and was nominally associated TARE (HR = 0.58; 95% CI 0.37–0.91; p = 0.019).

Conclusions: We found SBRT is associated with higher OS when compared to CRT or TARE for the treatment of unresectable ICC. Due to the retrospective nature of the study and potential selection bias, these findings should be evaluated prospectively.

© 2019 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Cholangiocarcinoma is the second most common primary hepatobiliary malignancy and accounts for over 7000 deaths annually in the United States [1,2]. Intrahepatic cholangiocarcinoma (ICC) comprises 10% of cholangiocarcinomas.1 Complete surgical resection offers the only possibility of cure for these patients, however only 12% of ICCs have resectable disease at diagnosis, accounting for one-third of patients with localized disease [3]. For the remaining patients with localized disease not amenable to surgical resection, several liver-directed treatment options exist, including conventionally fractionated external beam radiation therapy, chemoradiation (CRT), stereotactic body radiation therapy (SBRT), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) using yttrium-90 microspheres [4,5].

In part due to the rarity of the disease, there is no randomized evidence to guide decision making with regard to liver-directed therapies for unresectable ICC. Within radiation oncology, CRT has historically been the preferred treatment in the setting of hepatobiliary malignancies [6–9], but in more recent years SBRT and TARE have emerged as effective, conformal modalities that deliver high doses to tumor while limiting normal tissue toxicity [10]. The former modality employs hypofractionated external beam radiation and stereotactic immobilization, while the latter is a transcatheter intra-arterial procedure (typically performed by interventional radiology) that entails injection of yttrium-90 microspheres into the hepatic artery, thus capitalizing on the differential dependence of malignancy and normal parenchyma on hepatic arterial and portal venous blood supply, respectively.

* Corresponding author.
E-mail address: Dassy.DiazPardo@osumc.edu (D. Alexandra Diaz).
While there are retrospective studies comparing external beam radiotherapy to non-radiotherapeutic modalities [11], there are no studies comparing SBRT to conventional chemoradiation or TARE for this group of patients. We studied the overall survival of patients treated with SBRT, CRT, and TARE using the National Cancer Database (NCDB), a nationwide hospital-based registry accounting for 70% of newly diagnosed cancers in the United States.

2. Materials and methods

2.1. Study population

Using the NCDB, we identified patients with histologically- or cytologically-confirmed intrahepatic adenocarcinoma of the biliary tract diagnosed between 2004 and 2014. We included patients no more than 85 years old with a Charlson comorbidity score of 0–2. Patients who received surgery, had metastatic or lymph node-positive disease, or had missing T-stage or tumor size data, were excluded. Only patients who received CRT, SBRT, or TARE were included. SBRT was defined as external beam radiation therapy to a total dose of \( \geq 30 \) Gy delivered in \( \leq 5 \) fractions [12]. Patients who were treated with \(<5\) Gy per fraction with concurrent chemotherapy, defined as chemotherapy initiated within 14 days of radiation start, were allotted to the CRT group. Receipt of chemotherapy during the first line of treatment was permitted in the SBRT and TARE cohorts.

2.2. Statistical analysis

Patient characteristics were summarized by treatment groups using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Kruskal-Wallis tests were used to compare the differences in continuous variables among the treatment groups, while Chi-square tests or Fisher’s exact tests were used for categorical variables. Kaplan-Meier curves were generated and log-rank testing was used to compare the differences in overall survival among the treatment groups. To further study the association between treatment and overall survival, and to adjust for possible confounders, Cox proportional hazard models were used to estimate the hazard ratios between groups. Variables with statistically significant differences in distribution between the treatment groups were selected as covariates for Cox proportional hazards. Missing data was handled as a unique level for multivariable analysis. In order to rule out the potential biases from variables that predict for receipt of treatment, age, year of diagnosis, Charlson comorbidity score, vascular invasion, clinical T stage, tumor focality, and tumor size were used to generate propensity scores that were used to calculate inverse probability of treatment weights, which were accounted for in a weighted Kaplan-Meier analysis. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC).

3. Results

Fig. 1 shows the patient selection schema for the analyzed cohort. There were a total of 141 analyzable patients with unresectable ICC treated with SBRT (n = 27), CRT (n = 54), or TARE (n = 60). Table 1 shows the patient and disease characteristics of the cohort. SBRT, CRT, and TARE cohorts were respectively characterized by increasing proportion of patients with vascular invasion and tumor multifocality. ICC treated with TARE, specifically, was characterized by larger tumor size and higher T-stage, as well as more recent year of diagnosis. Roughly half of patients who received SBRT or TARE also received chemotherapy during the first course of treatment. The median dose and number of fractions for CRT was 50.4 Gy (interquartile range [IQR] 45–54 Gy) and 28 fractions (IQR 25–30), respectively. The median dose and number of fractions for SBRT was 45 Gy (40–50 Gy) and 5 fractions (IQR 3–5) respectively. Median follow-up time for all patients was 17 months. On univariate analysis, SBRT was associated with higher overall survival compared to CRT (hazard ratio [HR] = 0.37; 95% confidence interval [CI] 0.20–0.68; \( p = 0.001 \)) and TARE (HR = 0.40; 95% CI 0.22–0.74; \( p = 0.003 \)). There was no statistically significant difference in overall survival between patients treated with TARE and CRT (HR = 0.92; 95% CI 0.60–1.40; \( p = 0.69 \)) (Fig. 2). The median overall survival for patients treated with SBRT, TARE, and CRT was 48 months (95% CI 20, upper limit not reached), 20 months (95% CI 14–24), and 14 months (95% CI 11–20), respectively.
On multivariable analysis (Table 2), SBRT remained associated with higher overall survival when compared to CRT (adjusted HR = 0.44; 95% CI 0.21–0.91; p = 0.028) and TARE (HR = 0.42; 95% CI 0.21–0.84; p = 0.014). There was no statistically significant difference in overall survival with TARE when compared to CRT (HR = 1.04; 95% CI 0.58–1.86; p = 0.89). None of the other covariates tested on multivariable analysis had a statistically significant association with overall survival.

After excluding patients with missing covariates for propensity weighting, there were 19, 25, and 43 patients in the SBRT, CRT, and TARE cohorts, respectively. After propensity weighting adjustment, SBRT maintained a statistically significant higher overall survival compared to CRT (HR = 0.22; 95% CI 0.11–0.44; p < 0.0001) and was nominally associated with higher overall survival compared to TARE (HR = 0.58; 95% CI 0.37–0.91; p = 0.019) without reaching the Bonferroni-adjusted significance threshold (α = 0.017). There was again no statistically significant difference in overall survival between patients treated with TARE and CRT (HR = 1.05; 95% CI 0.67–1.63; p = 0.84) (Fig. 3).

### Table 1
Patient and disease characteristics of the analyzed cohort, stratified by radiotherapeutic modality.

| Characteristic               | SBRT              | TARE              | CRT              | P     |
|-----------------------------|-------------------|-------------------|------------------|-------|
| n (%)                       | 27 (100%)         | 60 (100%)         | 54 (100%)        |       |
| Age (Years)                 |                   |                   |                  | 0.11  |
| Median (IQR)                | 71 (61, 80)       | 65 (57.5, 74.5)   | 67 (61, 74)      |       |
| Sex                         |                   |                   |                  | 0.14  |
| Male                        | 18 (66.7%)        | 27 (45.0%)        | 25 (46.3%)       |       |
| Female                      | 9 (33.3%)         | 33 (55.0%)        | 29 (53.7%)       |       |
| Race                        |                   |                   |                  | 0.85  |
| White                       | 25 (92.6%)        | 51 (85.0%)        | 46 (85.2%)       |       |
| Black                       | 1 (3.7%)          | 2 (3.3%)          | 2 (3.7%)         |       |
| Other                       | 1 (3.7%)          | 7 (11.7%)         | 6 (11.1%)        |       |
| Charlson Comorbidity Score  |                   |                   |                  | 0.35  |
| 0                           | 17 (63.0%)        | 41 (68.3%)        | 39 (72.2%)       |       |
| 1                           | 9 (33.3%)         | 13 (21.7%)        | 14 (25.9%)       |       |
| 2                           | 1 (3.7%)          | 6 (10.0%)         | 1 (1.9%)         |       |
| Year of diagnosis           |                   |                   |                  | <0.0001 |
| Median (IQR)                | 2011 (2008, 2013) | 2013 (2011, 2014) | 2010 (2007, 2012)|       |
| T-stage                     |                   |                   |                  | <0.0001 |
| 1                           | 16 (59.3%)        | 18 (30.0%)        | 13 (24.1%)       |       |
| 2                           | 7 (25.9%)         | 34 (56.7%)        | 15 (27.8%)       |       |
| 3                           | 3 (11.1%)         | 8 (13.3%)         | 22 (40.7%)       |       |
| 4                           | 1 (3.7%)          | 0 (0.0%)          | 4 (7.4%)         |       |
| Tumor Size (cm)             |                   |                   |                  | <0.0001 |
| Median (IQR)                | 4.5 (3.2, 5.9)    | 6.5 (4.5, 9.2)    | 4.4 (2.9, 6.5)   |       |
| Vascular Invasion           |                   |                   |                  | 0.038 |
| No                          | 16 (59.3%)        | 23 (38.3%)        | 12 (22.2%)       |       |
| Yes                         | 7 (25.9%)         | 21 (35.0%)        | 22 (40.7%)       |       |
| Unknown                     | 4 (14.8%)         | 16 (26.7%)        | 20 (37.0%)       |       |
| Tumor Focality              |                   |                   |                  | 0.032 |
| Unifocal                    | 3 (11.1%)         | 19 (31.7%)        | 3 (5.6%)         |       |
| Multifocal                  | 17 (63.0%)        | 34 (56.7%)        | 24 (44.4%)       |       |
| Unknown                     | 7 (25.9%)         | 7 (11.6%)         | 27 (50.0%)       |       |
| Chemotherapy                |                   |                   |                  | 0.017 |
| No                          | 16 (59.3%)        | 27 (45.0%)        | 0 (0.0%)         |       |
| Yes                         | 11 (40.7%)        | 32 (53.3%)        | 54 (100.0%)      |       |
| Unknown                     | 0 (0 %)           | 1 (1.7%)          | 0 (0.0%)         | <0.0001 |

Abbreviations. SBRT- stereotactic body radiation therapy. TARE- transarterial radioembolization. CRT- chemoradiation. IQR- Interquartile range.

1. Mann-Whitney U (Wilcoxon rank-sum) test.
2. Chi-square test.
3. Fisher’s exact test.

#### Fig. 2.
Kaplan-Meier curves for overall survival, stratified by radiotherapeutic modality.

In what is, to our knowledge, the first study comparing outcomes of radiotherapeutic modalities for unresectable ICC, we found SBRT was associated with higher overall survival when compared to CRT or TARE. Importantly, these results were similar after adjusting for relevant prognostic and confounding variables.
including T-stage, tumor size, focality, and vascular invasion [13–15]. The rarity of ICC has complicated efforts to prospectively and comparatively evaluate radiotherapy modalities for nonsurgical management of unresectable disease, although several studies have shown promising results for individual techniques. Studies have shown a modest prognostic and palliative benefit associated with external beam therapy for ICC and hepatocellular carcinoma, the 37 institutional phase II study of high-dose hypofractionated proton beam therapy for ICC and hepatocellular carcinoma, the 37 patients with ICC had encouraging 2-year local control and overall survival of 73% versus 38% and a 3-year local control of 78% versus 45%. Median overall survival for the entire cohort was 30 months and median overall survival for the high-BED group, specifically, was not reached [12]. Additionally, in a multi-institutional phase II study of high-dose hypofractionated proton beam therapy for ICC and hepatocellular carcinoma, the 37 patients with ICC had encouraging 2-year local control and overall survival of 94.1% and 46.5%, respectively, after treatment with a maximum total dose of 67.5 Gy equivalent in 15 fractions. Median overall survival for the ICC group was 22.5 months [26]. Although we did not explicitly evaluate patients treated with hypofractionated regimens delivered in greater than 5 fractions, in comparison to the aforementioned studies, the SBRT patients in our study had a favorable median overall survival of 48 months. Such comparisons should be interpreted with caution, however, as the SBRT patients in our study have more favorable disease characteristics such as smaller tumor size and no prior therapy.

We also found that SBRT is associated with improved overall survival compared to TARE, a modality that theoretically offers high dose delivery and conformity. Retrospective evidence in the setting of hepatocellular carcinoma suggests that both modalities offer good pathologic response and minimal toxicity as a bridge to transplant [27]. However, although TARE is characterized by a high selectivity for tumor versus normal hepatic parenchyma, and potential to deliver high dose to tumor [28], it is limited by significant variability in absorbed dose [29–31]. It is unclear if our findings reflect this disadvantage, microenvironment-based resistance that is specific to ICC, superior vascular injury and ablation conferred by SBRT, or unrecognized selection bias. It is also worth noting that novel TARE techniques such as radiation segmentectomy, which permits further dose escalation and conformity compared to lobar infusion, have shown promising results in early-stage hepatocellular carcinoma [32,33] and may be a comparable alternative to SBRT for limited ICC in the future.

Despite adjustment for key confounders, there are limitations of this study that should be noted. First, the caveats associated with any retrospective study are inherent to this NCDB study, including possible selection bias and inability to account for a variety of potential confounders, such as performance status or departmental-clinical expertise. Along these lines, despite inverse probability of treatment weighting, variability in baseline characteristics such as tumor size and multifocality may reflect potential lead-time bias
and/or tumor biology that cannot be accounted for. Second, there is a lack of toxicity data provided for each of the modalities, and baseline liver function may play a role in modality selection and/or radiation dose choice. Furthermore, therapies might be chosen on the basis of anatomic location or radiologic appearance which serve as further confounders in this study. For example, a tumor along the inner edge of the liver might be less likely to receive SBRT due to concern of damaging adjacent bowel, or a tumor with an infiltrative pattern on MRI might be more difficult or poorly defined. Unfortunately, such detailed data regarding tumor location is not available through NCDB. The lack of dose and microsphere-type data for TARE is also limiting, as biologic effect is known to vary with dose and it is possible that response may vary with microsphere brand [34–36]. Also, we acknowledge that the statistical power of the study is limited by the relatively low patient numbers in each of the cohorts. Finally, the lack of local recurrence and toxicity data through the NCDB limits complete evaluation of the potential benefit of these modalities. Nevertheless, as the majority of patients with ICC die of tumor-related liver failure, survival is strongly correlated with local control [37].

In summary, we found SBRT was associated with higher overall survival when compared to CRT and TARE in the management of unresectable ICC. These findings suggest that for clinical scenarios amenable to any of these treatments, SBRT may be the preferred option. However, these results should be interpreted with caution given the possibility of selection bias, and these modalities should be compared prospectively to clarify the clinical conditions for which these modalities are best suited.

Funding disclosures

None

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This data was presented in part at the American Society of Radiation Oncology (ASTRO) Annual Meeting 2018 (San Antonio, TX).

References

[1] Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: liver, biliary tract, and pancreas. Gastroenterology 2009;136:1134–44. https://doi.org/10.1053/j.gastro.2009.07.036.
[2] Yao EJ, Jabbour S, Parekh N, Lin Y, Moss RA. Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. BMC Gastroenterol 2016;16. https://doi.org/10.1186/s12876-016-0527-z.
[3] Nakeeb A, Tran KG, Black MJ, Erickson BA, Ritch PS, Quebbeman EJ, et al. Improved survival in resected biliary malignancies. Surgery 2002;132:555–63. Discussion 563–564.
[4] Koay EJ, Odisio BC, Javle M, Vauthey J-N, Crane CH. Management of unresectable intrahepatic cholangiocarcinoma: how do we decide among the various liver-directed treatments? Hepatobil Surg Nutr 2017;6:105–16. https://doi.org/10.21037/hbsn.2017.01.16.
[5] National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed January 30, 2019. n.d.
[6] Foo ML, Gunderson LL, Bender CE, Buskirk SJ. External radiation therapy and transcatheter iodine in the treatment of extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 1997;39:929–35.
[7] Whittington R, Neuberg D, Tester WJ, Benson AB, Haller DG. Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a phase I Eastern Cooperative Oncology Group Trial. J Clin Oncol 1995;13:227-32. https://doi.org/10.1200/JCO.1995.13.1.227.
[8] Kopelson G, Harisides I, Trettter P, Chang CH. The role of radiation therapy in cancer of the extra-hepatic biliary system: an analysis of thirteen patients and a review of the literature of the effectiveness of surgery, chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1977;2:883–94.
[9] Crane CH, Macdonald KD, Vauthey JN, Yehuda P, Brown T, Curley S, et al. Limitations of conventional doses of chemoradiation for unresectable biliary...
Zeng Z-C, Wu YT, Zhu AX, Dawson LA, Hong TS. Radiation therapy for liver tumors: ready for inclusion in guidelines? Oncologist 2014;19:868–79. https://doi.org/10.1634/theoncologist.2014-0097.

Kolarich AR, Shah JL, George TJ, Hughes SJ, Shaw CM, Geller BS, et al. Non-surgical management of patients with intrahepatic cholangiocarcinoma in the United States, 2004–2015: an NCDB analysis. J Gastrointest Oncol 2018;9:536–45. https://doi.org/10.21037/jgino.2018.02.04.

Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol 2016;34:219–26. https://doi.org/10.1200/JCO.2015.61.3779.

Wright GP, Perkins S, Jones H, Zureikat AH, Marsh JW, Holtzman MP, et al. Surgical resection does not improve survival in multifocal intrahepatic cholangiocarcinoma: a comparison of surgical resection with intra-arterial therapies. Ann Surg Oncol 2018;25:83–90. https://doi.org/10.1245/s10434-017-6110-1.

Blechacz B, Konota M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512–22. https://doi.org/10.1038/nrgastro.2011.131.

Mavros MN, Economopoulos KP, Alexiou VC, Pavlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg 2014;149:565–74. https://doi.org/10.1001/jamasurg.2013.5132.

Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2008;72:1495–501. https://doi.org/10.1016/j.ijrobp.2008.07.016.

Chen V-Y, Zeng Z-C, Tang Z-Y, Fan J, Zhou J, Jiang W, et al. Determining the role of external beam radiotherapy in unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 84 patients. BMC Cancer 2010;10:492. https://doi.org/10.1186/1471-2407-10-492.

Zeng Z-C, Tang Z-Y, Fan J, Zhou J, Qin L-X, Ye S-L, et al. Consideration of the role of radiotherapy for unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 75 patients. Cancer J 2006;12:113–22.

Tse BV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase 1 study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. JCO 2008;26:657–64. https://doi.org/10.1200/JCO.2007.13.3529.

Kopek N, Holt M, Hansen AT, Høyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol 2010;94:47–52. https://doi.org/10.1016/j.radonc.2009.11.004.

Gkika E, Hallauer L, Kirsie S, Adelahr S, Bartl N, Neeff HP, et al. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. BMC Cancer 2017;17:781. https://doi.org/10.1186/s12885-017-3788-1.

Brunner TB, Blaich O, Lewitwicki V, Abbasi-Senger N, Mommm 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. Radiat Oncol 2019;14:22–7. https://doi.org/10.1186/s13058-019-1115-1.

Mohamed M, Kazi AW, Tejani MA, Sharma AK, Kashyap R, Noel MS, et al. Ablation of intrahepatic cholangiocarcinoma: a comparison between STSBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. Adv Radiat Oncol 2015;1:35–42. https://doi.org/10.1016/j.adro.2015.12.003.

Fox RA, Klemp PF, Egan G, Mina LL, Burton MA, Gray BN. Dose distribution following selective internal radiation therapy. Int J Radiat Oncol Biol Phys 1991;21:463–7.

Tong AKT, Kao YH, Too CW, Chin KFW, Ng DCE, Chow PKH. Yttrium-90 hepatic radioembolization: clinical review and current techniques in interventional radiology and personalized dosimetry. BJR 2016;89:20150943. https://doi.org/10.1259/bjr.20150943.

Kennedy AS, McNeillie P, Dezarn WA, Nutting C, Sangro B, Wernet D, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin 90Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys 2009;74:1494–500. https://doi.org/10.1016/j.ijrobp.2008.10.005.

Gulec SA, Mesoloras G, Dezarn WA, McNeillie P, Kennedy AS. Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: the tumor selectivity of the treatment as a function of tumor to liver flow ratio. J Transl Med 2007;5:15. https://doi.org/10.1186/1479-5876-5-15.

Riaz A, Gates VL, Atassi B, Lewandowski RJ, Mulcahy MF, Ryu RK, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys 2011;79:163–71. https://doi.org/10.1016/j.ijrobp.2010.06.027.

Lewandowski RJ, Gabr A, Abouchehal A, Ali R, Al Asadi A, Moria RA, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. Radiology 2018;287:1050–90. https://doi.org/10.1148/radiol.2018171768.

Claudio Traino A, Boni G, Mariani G. Radiosomometric estimates for radioembolic therapy of liver tumors: challenges and opportunities. J Nucl Med 2012;53:509–11. https://doi.org/10.2967/jnumed.111.100537.

Zhang Z, Fardanesh MR, Machac J, Heiba S, Knesaurek K, Zaretsky V, et al. Comparison of therapeutic response using RECIST criteria: Y-90 SIR-Spheres and TheraSphere treatment of unresectable hepatocellular carcinoma. J Nucl Med 2013;54:234.

Bhangoo MS, Karmani DR, Hein P, Giap H, Knowles H, Issa C, et al. Radioembolization with Yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. J Gastrointest Oncol 2015;6:469–78. https://doi.org/10.7373/jgio.2015.05.06.

Yamashita S, Koay EJ, Passot G, Shroff R, Raqiah RP, Conrad C, et al. Local therapy reduces the risk of liver failure and improves survival in patients with intrahepatic cholangiocarcinoma: a comprehensive analysis of 362 consecutive patients. Cancer 2017;123:1354–62. https://doi.org/10.1002/cncr.30448.