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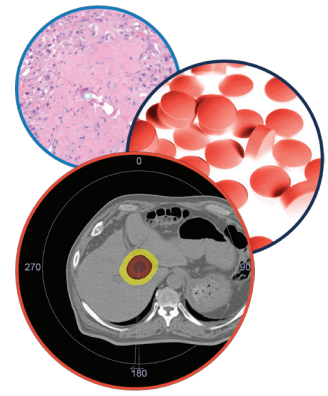

Hepatic Oncology

Chemoembolization versus radioembolization for the treatment of unresectable intrahepatic cholangiocarcinoma in a single institution image-based efficacy and comparative toxicity

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Summary points

- Comparative treatment-related adverse events from radioembolization or chemoembolization were statistically insignificant, and should therefore not be used to dictate the treatment modality.
- The tumor response rate and disease control rate from both radioemboization and chemoembolization were similar.
- Logistic regression did not reveal any background factor to independently associate with disease control after transarterial therapy.
- Both current and prior chemotherapy regimens did not have a significant effect on outcomes from the procedure.
- Eastern Cooperative Oncology Group score did not correlate with treatment response to either modality, although our study is limited by its retrospective nature and small patient population.

Aim: Compare radioembolization (Y90) and chemoembolization (CE) for the treatment of unresectable intrahepatic cholangiocarcinoma (UICC). **Materials & methods:** Institutional Review Board-approved, retrospective search was performed. Forty patients with UICC were treated with either Y90 (n = 25, 39 treatments) or CE (n = 15, 35 treatments). Comparative analysis was performed using Student's *t* and fisher-exact tests. Multivariable-logistic regression was also performed. **Results:** Median ages were 60 and 64 years for CE and Y90 groups, respectively (p = 0.798). Patient variables including age, Eastern Cooperative Oncology Group score, tumor burden, extra-hepatic disease, prior chemotherapy and prior surgery were similar between groups. Adverse events were similar in both groups (CE 20%, Y90 26%; p > 0.9). Overall response rate (CE 6%, Y90 4%; p > 0.9) and disease control rate (CE 46%, Y90 48%; p > 0.9) were statistically similar. Multilogistic regression did not identify any variables that correlated with disease control rate, including Eastern Cooperative Oncology Group score and tumor burden. **Conclusion:** Our observation shows that CE and Y90 display similar toxicity and disease control in the treatment of UICC.

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• radioembolization

Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy arising from the epithelial cells of intrahepatic bile ducts. It is the second most common primary liver malignancy after hepatocellular carcinoma (HCC) in the USA, with an annual age-adjusted incidence of 1–2 cases per 100,000 [1,2]. For patients with localized disease, hepatic resection is the standard of care [3,4]. The ability to achieve complete margin-negative surgical resection (RO resection margin) for node-negative disease may confer a 5-year survival range of 30–63% [5,6]. Unfortunately, <50% of patients present with early-stage disease that is suitable for surgical resection [7]. In addition, despite aggressive resection, at least 50% of patients undergoing resection experience recurrence of tumor with the mean time to recurrence being ranging from 10 to 20 months [8]. For these patients the prognosis is poor, with median survival ranging from 3 to 8 months [9,10].

Systemic therapy, particularly gemcitabine-based regimens, is frequently used for these patients with advanced ICC; however, the role of systemic chemotherapy is still evolving with the current regimens providing only modest survival benefit, with a reported response rate of 10–30% [11,12].

Table 1. Baseline patient characteristics.

Patient characteristics	CE	Y90
Number of patients	15	25
Age (years):		
– Median	60	64
– Range	38–89	29–87
Gender (n), %:		
– Male	8 (53%)	8 (32%)
Hepatitis (n)	3	9
ECOG score:		
– 0–2	14	24
– >2	1	1
Tumor extent (n):		
– 1–25%	2	12
– 26–50%	5	9
– 51–75%	2	0
– >75%	0	0
– Unknown	6	4
Extrahepatic disease (n)	4	11
Prior chemotherapy (n)	13	16
Concurrent chemotherapy (n)	5	4
Prior liver surgery/RFA (n)	4	5

Y90: Radioembolization; CE: Chemoembolization; ECOG: Eastern Cooperative Oncology Group; RFA: Radiofrequency ablation.

Over the years, arterially directed embolic therapy has increasingly been utilized for the treatment of this patient population. Hepatic arterial infusion (HAI), drug-eluting beads (DEB), radioembolization (Y90) and chemoembolization (CE) utilize differential perfusion physiology to treat liver tumors with minimal collateral damage [13]. Part of the optimism for this strategy is derived from the efficacy of this treatment in patients with HCC. Given that ICC is also a primary liver malignancy, there is reason to expect good response with intra-arterial therapy (IAT). While both Y90 and CE have been shown to be efficacious to treat unresectable ICC in this patient population, there are few studies that have reported on the safety and efficacy of these modalities [10,14–16], and there is insufficient evidence concerning the superior treatment device [8].

Given the challenge of obtaining good treatment response in this population, it is important to assess the comparative performance of these treatment modalities to optimize management and to direct the focus of future research in this arena. Herein, we compare the image-based efficacy (i.e, tumor response based on imaging) and toxicity of Y90 and CE for unresectable ICC in a single center setting. Being that cholangiocarcinoma is a relatively hypovascular tumor [17], we hypothesize that Y90 will perform better given that its efficacy is not dependent on embolization, but rather on local delivery of high-dose radiation.

Methods

• Patient selection

This study was Institutional Review Board approved. We performed a retrospective search for patients with unresectable ICC treated with IAT at our institution from August 2001 to July 2016. Forty consecutive patients were treated with either Y90 (n = 25) or CE (n = 15). A multidisciplinary team comprised of surgical oncologists, medical oncologists, radiation oncologists and interventional radiologists evaluated eligible patients to determine the type of therapy. Our pretherapy evaluation comprised of computed tomography (Siemens Healthcare) using 3–5 mm thick slices or MRI (Siemens Healthcare, IL, USA) using 3–10 mm thick slices. Tumor burden was assessed by evaluating target lesion size and number, presence of nontarget lesions and presence of lymph nodes on imaging. Patients were grouped according

to their index intra-arterial treatment modality regardless of treatment crossover. Forty consecutive patients were included in this study of which 15 patients were treated with CE and 25 patients were treated with Y90 (Table 1).

• Hepatic arterial therapy technique

CE technique was performed in a conventional fashion or using DEB. The specifics of the embolization device, embolic used and chemotherapeutic agents are listed in Table 2. Patients were typically planned for two to three treatment cycles based on the extent of liver tumor involvement. Treatments were spaced in 2–3-week intervals depending on patient toxicity. For Y90, visceral angiogram was performed to evaluate arterial anatomy and determine optimal placement of the microcatheter for embolization. 99mTC-labeled macroaggregated albumin was delivered through the hepatic artery to assess hepatopulmonary shunting and to detect hazardous extrahepatic deposition. Shunt fractions were calculated using planar scintigraphy. Y90 therapy was delivered as per manufacturer's recommendation [18]. Placement of the delivery microcatheter for both CE and Y90 was based on the extent and location of liver disease, and included whole liver, lobar or segmental treatment (Table 2).

• Study schedule & outcome measures

Toxicity was recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events version 3.0. Our follow-up protocol consisted of a CT or MRI scan within 1-month post-treatment. Tumor response rates were measured according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria [19]. Modified RECIST was specifically chosen because it had been shown to correlate with survival and it outperforms RECIST in this patient population [20]. Overall response rate refers to the combination of complete and partial responders per mRECIST. Disease control rate (DCR) refers to the combination of all responders and those with stable disease.

• Statistical analysis

An as-treated analysis was performed. The Student's *t* test was used for continuous data. The Fisher's exact test was used for categorical data comparisons (two-tailed). Multivariable logistic regression was used to evaluate the association between independent variables and DCR. DCR was chosen instead of overall response given the low response rate and the relatively small size of the study sample (a regression model based on overall response would be unacceptably biased). p-values <0.05 were considered statistically significant. All statistics were calculated using JMP software (JMP, SAS Institute, Inc, NC USA).

Table 2. Treatment factors.

Number of treatment courses	CE	Y90
	35	*39*
Type of treatment		
Conventional TACE (n)	24	0
Drug-eluting beads (DEB-TACE) (n)	7	2[†]
– Y90 theraspheres	4[†]	26
– Y90 SIR-spheres	0	11
– Total	4	37
Total hepatic bead treatment (n)		
1	5	13
2	5	11
3	4	0
≥4	2	1
Level of branching (n)		
Whole liver	1	0
Lobar	20	29
Segmental	14	4
Lobar/segmental	0	6
Y90 activity delivered	NA	1.56 GBq (0.41–5.31)

[†]Crossover treatment
Y90: Radioembolization; CE: Chemoembolization; DEB: Drug-eluting bead; TACE: Transarterial chemoembolization.

Results

• Patient characteristics

Forty consecutive patients were included. Fifteen patients were treated with CE and 25 patients were treated with Y90. Median age was similar between both groups; 60 years (range: 38–89) for CE and 64 years (range: 29–87) for Y90 (p = 0.798). Tumor extent (burden) was similar between the CE and 90Y groups (p > 0.9). The groups were also similar in the remaining characteristics including gender, Eastern Cooperative Oncology Group (ECOG) score, extrahepatic disease, prior chemotherapy, concurrent chemotherapy and prior liver surgery or ablation. Baseline characteristics are summarized in Table 1.

• Treatment factors & adverse events

Forty patients underwent 74 treatments (35 treatments in the CE group and 39 in the Y90 group). The majority of CE treatments were

performed in a conventional fashion (78%) with the remaining treatments using DEB loaded with doxorubicin (DEBDOX). Crossover treatments were performed in some patients if they did not respond to the initial treatment modality. In the CE group, there were four crossover treatments with Y90, while the Y90 group had two crossover treatments with DEBDOX. The majority of treatments in both groups were performed in a lobar fashion. The median Y90 activity delivered was 1.56 Gbq (0.41–5.31 Gbq). There were no reported cases of stasis with Y90 administration in the patient cohort.

Out of 33 treatments in the CE group, there were 7 (20%) treatment-related adverse events. Only three (9%) of those were high grade (≥grade 3). Out of 39 treatments in the Y90 group, there were 10 (26%) treatment-related adverse events with 4 (10%) being high grade. Overall and high-grade adverse events were similar in both groups ($p > 0.9999$). The most common side effects were fever and abdominal pain in the CE group and abdominal pain in the Y90 group. High-grade adverse events in the CE group were represented by one patient with severe abdominal pain, one with refractory ascites and one with severe nausea and fatigue. In the Y90 group, two patients had severe abdominal pain with nausea and vomiting, one developed a gastric ulcer and one had liver failure with ascites and encephalopathy.

• Treatment efficacy

Treatment response is summarized in Table 3. There was similar overall response rate for Y90 and CE (Y90 4%; CE 7%; $p > 0.999$). DCR was also similar between both groups (Y90 47%; CE 48%; $p > 0.999$). Logistic regression did not reveal any background factor to independently associate with disease control (Table 4). Only one patient in our study from the CE group was adequately downstaged for partial hepatectomy.

Discussion

ICC has demonstrated an increased incidence in the USA within recent years [21], with some authors citing a 128% increase in incidence from 1973–2012 [22]. This poses a challenging clinical problem. More than half of all patients present with unresectable disease [7] and have few effective options for management. For those patients who are suitable candidates, surgery is the standard of care and the only chance for a cure [23–25]. However, approximately 70% of patients who undergo curative-intent surgical resection will experience disease recurrence in <20 months [26]. Traditionally, treatments including systemic therapy alone or in combination with radiation therapy have been employed in these patients [5,9,11]. These options are not curative while the associated toxicity and impact on quality of life is substantial [27]. In response to this, locoregional IAT used for disease control or palliation is becoming increasingly common.

Two specific techniques, CE and Y90, have been increasingly used for treatment of unresectable ICC. A fairly recent multi-institutional pooled cohort analysis that showed that IAT (Y90 and CE) for advanced ICC was safe and led to good disease control in the majority of patients (86%) [28]. However, despite the radically different cellular mechanisms of action, there has not been a clear establishment of the performance of one treatment over the other. The relatively low toxicity, potential to treat patients with significant tumor burden and fewer side effects are perceived advantages of using Y90 embolization [29,30]. On the other hand, Y90 may provide less tumor necrosis than CE in patients with HCC [31], but this performance difference has not been shown in the ICC treatment population. Another disadvantage of Y90 is the singular available agent (Y90) for treatment. On the contrary, CE allows for a broader selection of

Table 3. Image-based treatment response and progression.

	CE	Y90	p-value
Response	n = 15	n = 25	
Complete response	0	1	> 0.9999
Partial response	1	0	0.38
Stable disease	6	11	> 0.9999
Progression of disease	4	7	> 0.9999
Death from disease	1	0	0.38
Unknown status	3	5	> 0.9999

Y90: Radioembolization; CE: Chemoembolization.

Table 4. Logistic regression for background variables affecting treatment outcomes.

Variable	Standard error	Chi square	p-value
Gender	-64.281998	133503.79	0.9996
Extent (1,2,3,4)$^{2-1}$	145.821079	398503.17	0.9997
Extent (1,2,3,4)$^{3-2}$	-159.08415	384289.85	0.9997
Extrahepatic disease	48.1877063	182038.24	0.9998
ECOG^{0}	108621.63	0.00	0.9999
ECOG^{1}	45677.54	0.00	0.9997
ECOG^{2}	300000.46	0.00	0.9998
Prior radiofrequency ablation/liver surgery	-61.047392	63269.132	0.9992
Prior chemotherapy	245929.67	0.00	0.9996
Current chemotherapy	-61.793528	106602.59	0.9995
Locoregional therapy	-50.730397	88131.781	0.9995
Age	14936.628	0.00	0.9998

ECOG: Eastern Cooperative Oncology Group.

chemotherapeutic agents, which in turn enables tailored treatment for specific cancers, as is currently the trend in oncology [32–34]. Advocates for chemoembolization cite the above reasons as clear advantages favoring the use of CE for ICC; however, skeptics argue that ICC may not be vascular enough to enjoy the degree of efficacy reported in the HCC literature. Y90, whose treatment efficacy is likely not solely dependent on embolization, may be more ideal in the treatment of ICC and this reasoning drove our hypothesis. Given that chemoembolization and Y90 therapies are used interchangeably, there is a need to determine which therapy performs better with less adverse effects.

Our study did not reveal a significant difference in all-grade and high-grade toxicity in patients treated with CE or Y90. In general, both therapies were well tolerated with a low rate of high-grade toxicity (9–10%). The most common adverse events in our study across both modalities were abdominal pain, nausea, vomiting and fatigue, most of which were mild and resolved on their own with no delayed complications reported. This toxicity profile was in keeping with the rates reported in the literature [35]. The serious morbidities that we encountered, such as gastric ulcer (possibly from nontarget embolization), ascites and severe abdominal pain, are rare and within reported rates in systematic reviews for both CE and Y90 [30,36–38].

Our study also found that CE and Y90 achieved similar rates of tumor response and disease control in unresectable ICC. This finding may not be surprising to some, given that these treatments confer similar efficacy in other liver malignancies such as HCC [31]. We must indulge ourselves by saying that this observed parity in efficacy implies that the delivery of CE is not hindered by hypovascularity, which is a typical characteristic of ICC.

Both CE and Y90 have been evaluated on an individual basis for their efficacy in relation to many background variables. Good liver function, hypervascularity, solitary disease, tumor size (<8 cm) and previous systemic chemotherapy portend a favorable prognosis for CE [32–34]. For Y90, reported significant prognostic variables associated with an improved survival include a good ECOG performance status (ECOG 0), peripheral tumor morphology, no portal vein thrombosis, solitary disease and tumor burden ≤25% [29,30,39]. Our study did not find any background variables associated with treatment response, despite the findings reported in other studies. This finding could conceivably be due to the small sample size and must be taken in context.

Other types of IAT that have been used for ICC include HAI and bland embolization. HAI chemotherapy represents a therapeutic approach that combines delivery of high doses of chemotherapy directly to the arterial circulation where tumors derive most of their supply, minimizing the systemic toxicity of the chemotherapeutic agent [40]. Although this modality has offered good outcomes in terms of tumor response and survival [41], it is not as well tolerated as CE or Y90 [27]. Bland embolization is used preferentially over CE in some centers [42]; however, no large studies have been reported. A small number of patients (n = 13) treated with bland embolization were included

in a multi-institutional analysis of patients with advanced ICC treated with IAT [28]. Median overall survival was 14 months, similar to that observed in the groups of patients treated with chemoembolization and Y90 (p = 0.46). Although HAI and bland embolization show promise, how these therapeutic options compare to the more common modalities of CE and Y90 is still unknown.

There are several limitations to this study. First, this is a retrospective study and therefore susceptible to bias including selection and population. Second, the patient population is very small, and therefore not powered for progression-free survival or overall survival. Moreover, survival was not assessed because many patients were lost to follow-up, and less than half of the subjects reached the end point (death, progression-free survival).

Conclusion

Chemoembolization and Y90 have a similar toxicity profile and comparable image-based disease control for the treatment of unresectable ICC. Robust prospective studies are needed to further characterize the comparative performance of these intra-arterial therapies.

Future perspective

We believe that further discrimination between the role of Y90 and CE, and indeed other IAT will be determined by prospective, randomized controlled patient studies. In addition, current literature supports that continued development of these modalities will spark further investigation into the downstaging potential of Y90 and increased interest in the use of thermal ablation for the treatment of smaller lesions in cholangiocarcinoma. Use of imaging to explore microvascular density and angiogenesis biomarkers may help tailor treatment to the vascularity of the tumor. This could include, for example, dedicated sequences defining vessel size, vessel density and blood volume on contrast-enhanced MRI. More efficient collaboration and development of international registries will help spur even more research into this aggressive cancer.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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