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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

A Comparison of Yttrium-90 Microsphere Radioembolization to Hepatic Arterial Infusional Chemotherapy for Patients with Chemo-refractory Hepatic Colorectal Metastases

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Opinion statement

Patients with unresectable hepatic colorectal metastases who become chemo-refractory have limited treatment options. Systemic chemotherapies such as TAS102 and regorafenib have been used in the refractory setting, but with only modest improvement in overall survival compared to best supportive care. In patients with liver-only or liver-dominant disease, direct chemotherapy to the liver such as hepatic artery infusional (HAI) chemotherapy and radioembolization (yttrium-90 (Y90)) should be considered. Due to the difficulty of HAI therapy post Y90 for technical reasons, we recommend HAI therapy prior to Y90.

Introduction

Worldwide, colorectal cancer is the third most common cancer among males and the second most common among females with an estimated 1.4 million cases diagnosed annually [1]. In approximately 15% of these cases, patients have metastatic disease at the time of diagnosis, while 60% will subsequently develop liver metastases [2••]. Multi-agent systemic chemotherapy including cytotoxic agents such as oxaliplatin and irinotecan as well as targeted agents (VEGF and EGFR pathway inhibitors) is the standard of care for initial treatment and has shown improved survival. The majority of patients, however, develop chemo-refractory disease [3–7].

The management of patients with chemo-refractory disease remains controversial and includes several systemic agents such as TAS 102 and regorafenib. The median survival of chemo-refractory patients is approximately 5 months with systemic agents, offering only a minor improvement versus best supportive care [8•, 9•]. In a subset of patients with liver-only or liver-dominant disease, there are liver-directed therapy options which include hepatic arterial infusional (HAI) chemotherapy [10, 11] and embolization or radioembolization with yttrium-90 (Y90) microspheres [12, 13]. Liver-directed therapy offers the possibility of a more substantial increase in overall survival; however, there are no studies comparing outcomes between groups of patients contemporarily treated with either HAI chemotherapy or Y90 microspheres. Thus, we sought to compare oncologic outcomes in patients with chemo-refractory hepatic metastatic colorectal cancer treated at two separate centers with either HAI chemotherapy or Y90 microspheres.

Methods

Institutional review board approval was obtained for this study at each institution (Memorial Sloan Kettering Cancer Center (MSKCC) for the HAI group and Rutgers Cancer Institute (RCI) of New Jersey for the Y90 group). Patients with liver-only or liver-dominant (with limited extrahepatic disease) metastatic colorectal cancer who had progressed on standard systemic chemotherapy were identified at each institution. In the HAI group, all patients (n = 20) were selected based on RECIST 1.1 progression in the liver on standard systemic agents (5-fluouracil/leucovorin, oxaliplatin, and irinotecan) prior to HAI pump placement and treatment. In the Y90 group (n = 26), 18 out of the 26 (69%) patients had progression of disease by RECIST 1.1; 3 (11%) patients were considered chemo-refractory due to evidence of progression of disease that did not meet RECIST criteria (elevating carcinoembryogenic antigen (CEA), or increasing SUV on PET), and 5 (19%) patients were chemo-intolerant. Minimal extrahepatic disease was defined as fewer than five total extrahepatic lesions each up to 2 cm in diameter in the HAI series. All the patients were of ECOG

performance status 0–2. Patient demographic, clinicopathologic, and radiographic data were collected on these patients. Initial total hepatic tumor volume was separated into quartiles, where quartile 1 was defined as 0–25% of total liver volume, quartile 2 was 25–50% of total liver volume, quartile 3 was 50–75% of total liver volume, and quartile 4 was 75–100% of total liver volume.

Y90 microsphere treatment

All patients were treated with SIR-spheres ^{90}Y resin microspheres (Sirtex Medical, Lane Cove, NSW, Australia) at RCI of New Jersey. Before administration of radioembolization, each patient's case was reviewed in a multidisciplinary comprising medical, radiation, surgical, and interventional oncology services. Patients on systemic chemotherapy stopped therapy for at least 2 weeks before and 2 weeks after completion of all radioembolization procedures.

The radioembolization procedure was conducted as previously described [13]. Before undergoing treatment, each patient underwent physical examination and had laboratory data: complete blood count, serum chemistry panel, liver function tests, coagulation panel, and CEA levels. All the patients had baseline imaging in the form of a triphasic contrast-enhanced CT scan or MRI of the abdomen as well as a PET-CT scan.

Triphasic CT of the abdomen was used for radiation treatment planning. Liver and tumor volumes were contoured manually and calculated for each patient using the Varian Eclipse (Palo Alto, CA) treatment planning software. The body surface area method was used for dose calculations [14].

During the first stage of the procedure, each patient had a hepatic angiogram from a right common femoral artery approach, which was used to evaluate the hepatic vascular anatomy and blood supply to the hepatic metastases. During hepatic angiography, coil embolization of the gastroduodenal artery, the right gastric artery, and other extrahepatic collateral vessels was performed, followed by intra-arterial delivery of technetium-99-labeled macroaggregated albumin (Tc-99-MAA). Following Tc-99-MAA injection, each patient underwent scintigraphy to evaluate for shunting from the hepatic arterial system to the pulmonary venous system, and to look for extrahepatic activity. A lung shunt fraction greater than 20% precluded Y90 administration. The pulmonary shunt fraction was then used to calculate the total dose, which was modified based on prior chemotherapy administration. The determined dose of Y90 resin microspheres was then injected into the proper hepatic artery for whole liver treatment, or selectively into the right and left hepatic arteries in separate sessions for lobar treatments.

Shortly after radioembolization, each patient underwent a SPECT scan to obtain images produced by bremsstrahlung radiation released from the microspheres. This was used to confirm that the radiation microspheres were delivered to the liver.

HAI chemotherapy treatment

All patients in the HAI group were treated at MSKCC. Evaluation of patients for HAI therapy included CT arteriography to evaluate the hepatic arterial anatomy and extent of disease. Surgical placement and evaluation has been described

elsewhere [15]. After surgical placement of the pump, injection of Tc-99-MAA through the side port was done to ensure perfusion of the liver and to ensure no extrahepatic perfusion. Floxuridine (FUDR) and dexamethasone (dex) were inserted into the pump and infused over 14 days as previously described [16, 17]. After 14 days, the pump reservoir was accessed and emptied of all remaining drug and filled with heparin and saline to be infused over 14 days. Select patients received concurrent systemic chemotherapy every 2 weeks with irinotecan, 5FU/leucovorin, or anti-EGFR agents. Importantly, none of the patients in this group received a new systemic therapy, and all the patients had documented RECIST 1.1 progression on prior systemic therapies.

Patient follow-up

Patients were followed at each institution according to their respective practices. For the Y90 microsphere group, each patient was initially seen 2 weeks after the procedure, where physical examination and follow-up laboratory values were obtained. The Y90 patients were followed at 3-month intervals including CT of the chest, abdomen, and pelvis along with laboratory data. The HAI patients were followed at 2-month intervals including CT of the chest, abdomen, and pelvis, and every 2 weeks with laboratory data.

Data were gathered for each patient in the form of lesion analysis on pre- and post-procedure triphasic CT imaging and in calculation of overall survival. Imaging analysis of target lesions was performed using the RECIST1.1 criteria [18]. Partial response, complete response, and stable disease were also defined according to RECIST1.1.

Outcomes and statistical analyses

Fisher's exact test and the Wilcoxon rank-sum test were used to compare patient characteristics between the two groups. Overall response rate (ORR) was defined as complete and partial responses and exact 95% confidence intervals were presented. Overall survival (OS) was calculated from date of treatment to date of the last follow-up and estimated using Kaplan-Meier methods. To compare survival rate at a specific time point, a Wald test was used. The standard errors of the survival rates were calculated using Greenwood's formula. Multivariate Cox regression model was used to examine OS between the groups adjusting for age, gender, extrahepatic disease prior to treatment, and number of lines of previous chemotherapy. Log-rank analyses were used to compare overall survival stratified by the variables gender and presence of extrahepatic disease. All p values were based on two-tailed statistical analysis and p value <0.05 was considered to indicate statistical significance. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

A total of 20 patients treated with HAI chemotherapy were compared to 26 patients who were treated with Y90 microspheres. A comparison of patient demographics is listed in Table 1. The two groups were similar with respect to

Table 1. Comparison of patient demographics and clinical characteristics

Characteristics	Y90 (RCI) *N* = 26	HAI (MSKCC) *N* = 20	*p* value
Median age at diagnosis (range)	58.3 (32–74)	54 (18–75)	0.156
Gender			0.072
Male	18 (69)	8 (40)	
Female	8 (31)	12 (60)	
Extrahepatic disease present	12 (46)	4 (20)	0.117
Previous lines of chemotherapy, median (range)	2 (2–5)	4 (2–5)	<0.0001
Baseline tumor volume (quartile mean)	1.7	1.8	0.9576
Total number of treatments			
Quartile 1 (0–25%)	15 (58)	10 (50)	
Quartile 2 (25–50%)	6 (23)	5 (25)	
Quartile 3 (50–75%)	4 (15)	4 (20)	
Quartile 4 (75–100%)	1 (4)	1 (5)	

Numbers in parentheses are percentages, unless otherwise specified

age and gender, although the Y90 group contained a greater percentage of males (Y90 69% versus HAI 40%, $p = 0.072$). The number of previous lines of chemotherapy given prior to HAI or Y90 treatment was also compared, with the patients in the HAI group being more heavily pretreated compared to those in the Y90 group (median 4.00 (range 2–5) HAI versus 2.00 (range 2–5) Y90, $p < 0.0001$). Baseline tumor volumes were compared by quartiles (1–4), and there was no significant difference in the distribution of tumor volume quartiles between the two groups ($p = 0.958$). The Y90 group contained more patients with extrahepatic disease (EHD) compared to the HAI group (46 versus 20%), but this was not statistically significant ($p = 0.117$).

At the time of analysis, the median follow-up time among survivors was 62 months for the HAI group and 45 months for the Y90 group. Response to treatment by the RECIST criteria is listed in Table 2. In the

Table 2. Comparison of response by RECIST 1.1

Response by RECIST	Y90 *N* = 26	HAI *N* = 20
Partial response	0	6
Complete response	1	0
Stable disease	0	9
Progression	25	9
Overall response rate, % (95% CI)	4 (1–20)	75 (50–91)

HAI group (n = 20), there were 6 patients with a partial response (30%), 0 patients with a complete response, and 9 patients with stable disease (45%). In the Y90 group (n = 26), by the most recent post treatment scan, 0 patients had a partial response, 1 patient had a complete response (4%), and 0 patients had stable disease. The overall response (partial and stable disease) was 75% (95% CI 50–91%) versus 4% (95%CI 1–20%) in the HAI versus Y90, respectively.

The patients in the HAI group had longer median OS compared to those in the Y90 group (20.08 (95%CI 7.2–25.8) months versus 9.67 (95%CI 5.9–12.8) months, respectively), but the survival advantage was not uniform over time. As shown in Fig. 1, the advantage of the HAI group was greatest in the mid-range of the survival times, whereas the survival rates were more similar at both earlier and later times. An overall test of survival differences using a log-rank test yields a non-significant two-sided p value of 0.171 (Table 3). However, in comparing the two groups at 18 months, there was a very large difference. Specifically, the 18-month survival rate for the HAI group was 0.50 (standard error 0.11) versus 0.23 (standard error 0.08) for the Y90 group. There

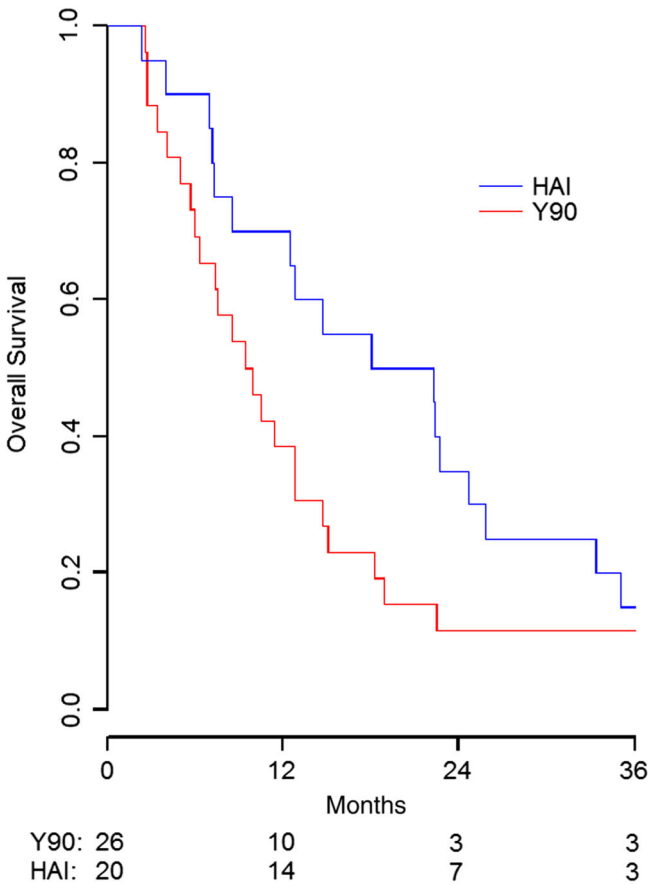

Fig. 1. Kaplan-Meier plot of overall survival. The median overall survival for patients treated with HAI (N = 20) was 20.1 versus 9.7 months for patients treated with Y90 (N = 26, p = 0.171).

Table 3. Comparison of survival outcomes

	Median OS, months (95% CI)			
	Y90 *N* = 26	*p* value	HAI *N* = 20	*p* value
Comparison between centers	9.7 (5.9–12.8)		20.1 (7.2–25.8)	0.171
Gender		0.033*		0.675*
Male	6.8 (4.1–10.5)		18.5 (4.0–34.9)	
Female	13.7 (7.5–NR)		20.1 (7.0–33.3)	
Extrahepatic disease present		0.143*		0.004*
Yes	9.7 (3.3–12.8)		7.7 (2.3–14.6)	
No	9.5 (5.0–22.4)		22.5 (12.5–33.3)	

CI confidence interval, *NR* not reached
**p* value comparing patient characteristics within each cohort

was a borderline significant difference between the survival rates at 18 months (unadjusted p value = 0.061) between the two treatment groups.

We stratified OS in each group by the variables gender and presence/absence of extrahepatic disease (EHD) (Table 3). Males treated with Y90 had significantly lower survival than females treated with Y90 (6.8 versus 13.7 months, p = 0.033). There was no significant difference in survival between patients with respect to presence or absence of EHD at time of treatment initiation in the Y90 group (9.7 versus 9.5 months, p = 0.143). However, in the HAI group, patients with EHD were associated with shorter survival times than those that did not (4.7 versus 22.5 months, p = 0.004).

From the multivariate model, the HAI patients had a reduced hazard of death over time (HR 0.58 (95%CI 0.22–1.53)). This indicated that despite patients treated with HAI had reduced hazard of death over time, there was no significant difference in OS (p = 0.276).

Clinical toxicity

There were no complications related to HAI pump placement or pump function in this group of patients. In all but one patient, treatment was stopped due to progression or FUDR-associated liver toxicity (elevated alkaline phosphatase, AST, or hyperbilirubinemia). One patient stopped FUDR due to nearly complete regression of hepatic lesions radiographically.

Four out of 20 (20%) patients required a 50–75% dose reduction by the second cycle due to elevated liver function tests, and 17/20 (85%) required a dose reduction after the third cycle, which is consistent with dose reductions in other published HAI studies [1, 2••, 3, 4]. None of the 20 patients in this report required biliary stents or developed long-term liver or biliary toxicity.

The following complications were observed in the Y90 group: fatigue (n = 3), thrombocytopenia (n = 1), gastric ulcer (n = 2), and increased LFTs (n = 2). All were CTCAE 1 or 2.

Discussion

Metastatic colorectal cancer remains a significant clinical problem in oncology as it is the second most common cause of cancer-related death worldwide [1]. While surgical resection offers the most impact on survival, the majority of patients have unresectable disease [19]. Advancements in chemotherapy, including the addition of oxaliplatin and irinotecan to fluorpyridimine-based regimens as well as the addition of targeted therapies, have improved survival and remained the standard of care for chemotherapy-naïve patients [20]. Epidermal growth factor inhibitors, cetuximab and panitumumab, in combination with FOLFIRI or FOLFOX as first-line treatments for patients with RAS wild-type metastatic colorectal cancer have led to 29- and 30-month median survival in RAS wild-type patients, respectively [21, 22]. However, the use of anti-EGFR is limited to patients with RAS wild-type metastatic colorectal cancer, which occurs in approximately 45% of patients [23]. Emerging data have also demonstrated further limitation of anti-EGFR therapies to left-sided colorectal tumors [24, 25]. Furthermore, the majority of patients will eventually develop chemo-refractory disease where the median survival for best supportive care is approximately 4–6 months [8•, 9•].

Several treatment options exist for patients with chemo-refractory disease including chemotherapeutic agents. TAS 102 and regorafenib have both been evaluated versus best supportive care in phase III randomized trials in the refractory setting; however, increase in survival of approximately 1.5 months is mild at best [8•, 9•]. Regional chemotherapy with floxuridine (FUDR) administered continuously by HAI has been extensively studied in patients with metastatic colorectal cancer in both adjuvant and metastatic settings, and has shown improvements in response rates and overall survival [17, 26–28]. Hepatic metastases derive their blood supply almost exclusively from the arterial system allowing FUDR to be administered directly into the liver at high doses due to the first pass metabolism [29, 30].

In patients with unresectable hepatic metastases, regional chemotherapy in combination with systemic (oxaliplatin- or irinotecan-based regimens) has been shown to increase surgical resection rates (47% compared to 15% historical controls treated with systemic therapy only) [2••, 11]. In both of these studies, previously treated patients were included with reported median survivals being 32 and 35 months, respectively. In patients who are able to have liver metastases resected, adjuvant treatment with HAI plus systemic chemotherapy has produced 5-year survival as high as 78% [31••]. In this series, the median survival of patients treated with HAI (20.1 months), while significantly greater than our Y90 cohort, is substantially lower than the 32 and 35 months previously reported [11, 32]. All the HAI patients included in this series had RECIST-refractory disease to all standard chemotherapies; thus, they represent a subset of patients with metastatic colorectal cancer in whom reported survival rates are approximately 4 to 6 months [8•, 9•].

Selective internal radiation therapy (SIRT) with Y90 microspheres combined with systemic chemotherapy has been studied in the first-line setting. Although there was no significant difference in median progression-free survival, patients treated with FOLFIRI plus SIRT had a hepatic progression-free survival of 20.5 versus 12.6 months for patients treated with SIRT alone ($p = 0.02$) [33••]. SIRT has been found to be well tolerated with median overall survivals ranging from 10 to 12.5 months [12, 34, 35]. The median survival of our Y90 microsphere group of 9.7 months is consistent with these data.

A comparison of the outcomes in this study would indicate that while treatment with HAI chemotherapy is associated with a longer median survival than Y90 microspheres (20 versus 9.7 months, respectively), this was not statistically significant. The small sample size may limit the potential to achieve a significant *p* value. Nonetheless, the apparent divergence of the survival curves at approximately 20 months (Fig. 1) suggests that there may be a temporary early benefit to the HAI treatment.

Due to the differences in the timing of imaging q2 months in the HAI group and q3 months in the Y90 group, we are not able to accurately report on the progression-free survival.

There are a number of limitations of this study that should be considered when interpreting the data. This is a retrospective, non-case matched study comparing two sets of a small amount of patients treated with different therapies at two independent institutions. Nonetheless, no comparative studies such as this exist in the literature. We attempted to control for variables that could affect survival, such as percent of the liver involved by tumor, number of previous lines of chemotherapy, and percent of extrahepatic disease [11, 36]. For percent liver involvement by tumor, the two groups were not significantly different; however, for number of previous lines of chemotherapy, the HAI group had a significantly higher amount of previously treated patients, and this may explain why there is a relatively low median survival in this group than have been reported in other HAI chemotherapy studies [2••, 11]. In addition, another limitation of the study is the issue of systemic therapy following either HAI or Y90 treatment. In the HAI group, all the patients had RECIST 1.1 progression on prior systemic chemotherapy but continued to receive systemic therapy (no new systemic therapies were added), while in the Y90 group, some of the patients were continued on systemic therapy. Lastly, response rates were assessed according to the RECIST 1.1 criteria, which may not be the most adequate method to measure response for liver-directed therapies.

Given the available data, it would seem that patients with hepatic colorectal metastases (and limited extrahepatic disease) who become chemo-refractory to standard systemic chemotherapy should be considered for liver-directed therapy. Before treatment with Y90, arterial branches such as the right gastric and gastroduodenal artery are embolized to prevent extrahepatic delivery of the Y90 beads to the gastrointestinal tract [37], which may preclude subsequent use of HAI. During surgical placement of an HAI pump, the catheter tip is placed at the origin of the gastroduodenal artery, which has to be open to allow flow [38]. Therefore, if liver-directed therapy is being considered, HAI should be done before Y90 since the integrity of the gastroduodenal artery may be compromised after Y90 treatment. HAI is difficult to perform after Y90. Results from this study demonstrate the utility of liver-directed therapy with HAI or Y90 in patients with refractory metastatic colorectal cancer. Further studies are needed

to determine the benefit of one liver-directed therapy over another; randomized trials comparing the use of these two treatments should be considered.

Compliance with Ethical Standards

Conflict of Interest

Andrea Cercek declares that she has no conflict of interest.
Vyacheslav Gendel declares that he has no conflict of interest.
Salma Jabbour declares that she has no conflict of interest.
Dirk Moore declares that he has no conflict of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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