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Y90 Clinical Data Update: Cholangiocarcinoma, Neuroendocrine Tumor, Melanoma, and Breast Cancer Metastatic Disease

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While the most compelling levels of evidence for the use of Yttrium-90 (^{90}Y) radioembolization are in patients with hepatocellular carcinoma and hepatic metastases from colorectal cancer, a growing body of literature supports its use in other primary and secondary hepatic malignancies. This includes intrahepatic cholangiocarcinoma, as well as hepatic metastases from neuroendocrine cancer, ocular melanoma, and breast cancer. While is it not feasible to conduct prospective, randomized trials for radioembolization in the setting of these malignancies due to the low overall prevalence of liver-only disease, numerous single-arm studies in the last several years make a compelling argument for its use in select situations. This clinical update summarizes those findings.

KEYWORDS radioembolization, liver metastases, breast cancer, cholangiocarcinoma, melanoma, neuroendocrine, hepatic-arterial therapy, selective internal radiation therapy

Intrahepatic Cholangiocarcinoma

While radioembolization has robust support for primary hepatic malignancy, its focus has traditionally been on hepatocellular carcinoma. Cholangiocarcinoma is a rare malignancy that arises from epithelial cells of the biliary system, and accounts for less than 15% of primary hepatic malignancies. Furthermore, the majority of presentations are within the hepatic hilum or extrahepatic bile ducts, where hepatic arterial therapy has no role. Intrahepatic cholangiocarcinoma (ICC), which constitutes the remaining 10% of cholangiocarcinoma cases, involves the formation of a mass within the liver parenchyma, likely initially arising from small intrahepatic bile ducts.[1]

Prognosis is usually poor with relatively few treatment options. Only a minority of patients with ICC are candidates for surgical resection. Even when negative surgical margins (R0) are achieved, the 5-year overall survival rate is only 30%.[2] Systemic chemotherapy, consisting of a combination of gemcitabine and cisplatin, is typically offered for nonsurgical candidates, with limited survival benefit. Given the poor long-term overall survival and relative lack of systemic treatment options, radioembolization can play a pivotal role in appropriately selected patients. Both resin (SIR-sphere, Sirtex, Australia) and glass (TheraSphere, BTG, Canada) ^{90}Y microspheres have shown efficacy in patients with ICC.

Several studies regarding the use of radioembolization in ICC have been published (Table 1). Mouli et al have reported on the largest series in this population, with 46 patients.[3] The patient population represented a relatively advanced stage of ICC, with multifocal tumors in 35%, portal vein tumor thrombus in 24%, and extrahepatic metastases in 35%. Also, 35% of patients had received prior chemotherapy, and the remainder were deemed not fit to undergo systemic chemotherapy. Glass microspheres were used, with a target dose of 120 Gray to perfused tissue. Despite the advanced stage of these patients, significant hepatotoxicity was seen in less than 10% of patients, and treatment was well tolerated. Objective tumor response was seen in the vast majority of patients, with only 2% having initial disease

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Table 1 Studies Assessing Effectiveness of ^{90}Y Radioembolization for Intrahepatic Cholangiocarcinoma

Study	Device	Patients, *n*	Extrahepatic Disease	Prior Chemotherapy	Child-Pugh Score	Tumor Type	PVT	Radiologic Response (CR + PR), Criteria Used	Survival (Months)*
Ibrahim[21]	Glass	24	33%	29%	NR	46% solitary; 54% multifocal	38%	86% EASL; 27% WHO	14.9
Saxena[22]	Resin	25	48%	68%	NR	20% unilobar; 80% bilobar	0	24% RECIST	9.3
Hoffman[4]	Resin	33	24%	79%	NR	30% solitary; 70% multifocal	0	36% RECIST	22
Mouli[3]	Glass	46	35%	35%	NR	65% solitary; 35% multifocal	24%	73% EASL; 25% WHO	14.6 solitary; 5.7 multifocal
Camacho[5]	Resin	21	NR	NR	85% A; 15% B	48% <5; 52% >5	NR	37.5% mRECIST	16.3
Manceau[7]	Glass	40	0%	0%	97% A; 3% B	51% solitary; 49% multifocal	23%	96% EASL	28.6
Jia[23]	Resin	24	13%	100%	75% A; 25% B	NR	NR	36% mRECIST	9.0
Mosconi[6]	Resin	23	9%	52%	NR	9% solitary; 91% multifocal	17%	15% RECIST; 45% mRECIST	17.9

CR, complete response; NR, not reported; PR, partial response; PVT, portal vein thrombosis.
*Survival measured from time of ^{90}Y treatment.

progression after treatment. In survival assessments, multiple factors were deemed to be poor prognostic indicators: multifocal tumor, infiltrative tumor, and higher tumor burden (>25%). Portal vein invasion and the presence of extrahepatic metastases did not portend a poorer prognosis, suggesting that radioembolization should be considered even in those with extrahepatic metastases.

Promising results with resin ^{90}Y microspheres have also been reported. Hoffman et al reported the largest series of 33 patients treated with resin ^{90}Y for ICC.[4] All patients had portal vein patency, and 79% had received prior systemic chemotherapy. When patients were stratified by response rate, the tumor response rate (using RECIST criteria) was found to correlate with overall survival. Response rates using modified RECIST criteria with specific assessment of delayed-phase imaging within the first several months are a stronger predictor of overall survival compared to standard RECIST size measurements, suggesting that this imaging criteria using residual enhancement be used in future assessments.[5,6]

Given that many patients who undergo radioembolization for ICC have been exposed to gemcitabine which is a known radiosensitizer, a greater potential for hepatic toxicity exists. To date, no studies have assessed differences in toxicity rates in those who have received gemcitabine vs those who have not in the setting of ICC. Regardless, caution must be taken in timing liver-directed therapy with systemic chemotherapy. Manceau et al studied 35 patients retrospectively who underwent radioembolization as first-line therapy in conjunction with a gemcitabine-based chemotherapy regimen.[7] Permanent liver toxicities were observed in 17% of the study population. Despite this, median overall survival was 29 months for the entire cohort, and 53 months in patients with Child-Pugh A5 cirrhosis.

Neuroendocrine Tumor Metastases

Neuroendocrine tumors (NETs) primarily metastasize to the liver and may present with hormone-induced symptoms such as flushing and diarrhea. Most patients are not candidates for ablation or surgical resection, as metastatic NETs usually present with multifocal disease. Transarterial bland embolization, chemoembolization, and radioembolization have all shown high rates of tumor response with durable tumor control.[8] Transarterial therapy has traditionally been used for low- and medium-grade hepatic tumors that are not symptomatically controlled by somatostatin. Aggressive tumor subtypes, those with a Ki-67 index of greater than 20%, are typically initially treated with systemic chemotherapy. Although multiple criteria differentiate tumor aggressiveness, arterial embolization can safely and effectively be performed in any NET grade or origin.

Although no proven survival benefit has been shown with radioembolization compared with other embolic therapies such as bland particle embolization or chemoembolization, most studies have very heterogeneous populations, with inherent institutional selection biases with regard to patient selection. Radioembolization has numerous advantages over other hepatic arterial base therapies, making it a preferable

option in many scenarios. It is associated with lower rates of systemic toxicity such as postembolization syndrome and carcinoid crisis, and therefore can be routinely performed on an outpatient basis. Because it is a minimally embolic therapy with a smaller particle size, arterial vasculature remains preserved, allowing for future treatments. This is especially pertinent to the NET patient, who may require numerous treatments over several years. In the setting of previous biliary intervention contributing to sphincter of Oddi disruption, such as a Whipple procedure commonly performed for pancreatic head tumors, there is a higher risk of biloma and abscess formation after embolization. In these cases, radioembolization is a more suitable treatment choice due to its minimally embolic effect.[9]

Numerous studies on the use of radioembolization for NET metastases have shown prolonged tumor response correlating with extended overall survival. Kennedy et al reported on the one of the earliest series of patients, with 148 undergoing resin microsphere radioembolization. A median survival of 70 months was achieved in their cohort.

Prognosis after radioembolization depends on both baseline treatment characteristics as well as treatment parameters. Poor patient performance status, high tumor burden, and pre-existing hepatic dysfunction portend a worse prognosis after treatment.[10,11] With the advent of defined cutoffs for tumor aggressiveness using a Ki-67 index, significant differences in overall survival have been observed between well-differentiated and poorly differentiated tumors.[8,12] With regards to treatment, tumor absorbed dose has been shown to correlate with radiographic response, with tumor doses in excess of 191 Gray demonstrating a 93% specificity for tumor response.[13]

Regardless of therapy, the survival rate is very promising, with average survival in many cohorts exceeding 5 years. When treating a patient with metastatic NETs, one must keep average survival rates in mind and preserve both hepatic functions for the long term and arterial vasculature to allow for repeat treatments. Cirrhosis-like morphology of the liver can occur in greater than 50% of patients treated with whole-liver radioembolization, although most remain clinically asymptomatic.[14]

Ocular Melanoma

Ocular (uveal) melanoma has a predilection to metastasize to the liver. These are often widespread with a poor prognosis, and liver failure is the primary cause of death in these patients. Given the extent of disease in this group of patients, surgical resection and other liver-directed therapies such as thermal ablation are rarely an option. Due to the poor prognosis and limited systemic options available, transcatheter arterial-directed therapies have been increasingly utilized to control tumor growth and prolong survival. In many cases, hepatic arterial therapy, including radioembolization, should be offered as first line therapy for hepatic metastases, due to the limited results with systemic agents.

The first report of metastatic ocular melanoma treatment came from Kennedy et al who reported a retrospective review of 11 patients receiving 12 radioembolization treatments.[15] All patients had bilobar disease and more than 4 lesions. The

Table 2 Studies Assessing Effectiveness of ^{90}Y Radioembolization for Neuroendocrine Tumor Metastases

Study	Device	Patients, *n*	Extrahepatic Disease	Prior Chemotherapy	Site of Primary	Tumor Grade	Tumor Burden	Radiologic Response (CR + PR), Criteria Used	Survival (Months)*
Kennedy	Resin	148	NR	NR	67% small bowel; 19% pancreas	NR	NR	63% RECIST	70
Fan[24]	Glass	38	39%	39%	29% bowel; 37% pancreas	45% G1; 16% G2/G3; 39% Unknown	11% with greater than 66%	26% RECIST	29.2
King[25]	Resin	34	59%	16%	32% small bowel; 25% pancreas	NR	NR	50% RECIST	27.6
Memon[10]	Glass	40	35%	8%	25% small bowel; 23% pancreas	NR	5% with greater than 50%	64% WHO; 64% EASL	34.4
Cao[11]	Resin	58	43%	33%	36% small bowel; 26% pancreas	52% G1; 24% G2; 24% G3	10% with greater than 50%	50% RECIST	36.0
Saxena[12]	Resin	48	48%	52%	31% small bowel; 31% pancreas	63% G1; 21% G2; 17% G3	32% of total liver volume	55% RECIST	35.0
Paprottka[26]	Resin	42	NR	43%	55% small bowel; 21% pancreas	NR	14% with greater than 50%	23% RECIST	NR

CR, complete response; NR, not reported; PR, partial response.
*Survival measured from time of ^{90}Y treatment.

median survival was not reached at end of the study period; however, survival at 1 year was 80%. In comparison, a report of the Collaborative Ocular Melanoma Study Group found a median time from diagnosis of metastasis to death of <6 months and a death rate of 80% at 1 year and 92% at 2 years following report of melanoma metastasis.[16]

Gonsalves et al reported a series of 32 patients who underwent radioembolization therapy for melanoma hepatic metastasis.[17] The median overall survival was 10.0 months, and progression-free survival of hepatic metastasis was 4.7 months. Patients with tumor burden <25% had longer median overall survival (10.5 vs 3.9 months, $P = 0.0003$) and progression-free survival (6.4 vs 3.0 months, $P = 0.03$) than patients who had a pretreatment tumor burden of 25% or greater.

Due to the relatively low incidence of this disease, prospective randomized controlled trials are not feasible in this setting. However, a recently published retrospective comparative study of 58 patients was published. Xing et al compared 28 patients who underwent radioembolization vs 30 patients who received best supportive care.[18] Median overall survivals from diagnosis of hepatic metastases were 19.9 and 4.8 months for radioembolization and best supportive care, respectively ($P < 0.0001$).

Metastatic Breast Cancer

Breast cancer is the second most common malignancy worldwide. While the majority of patients present with early stage breast cancer, which is often amenable to curative treatments, many patients may initially present with or will progress to advanced metastatic disease. The pattern of breast cancer metastases is variable, with lymph nodes, lung and bone being the primary sites. Both hormonal and systemic chemotherapy have very established roles in this setting. A small percentage of patients will have liver-only metastases, or may have hepatic progression despite control of extrahepatic disease. These patients have typically been exposed to numerous chemotherapy regimens, yet will often remain very functional and have normal hepatic function clinically. In these patients, several studies have shown promising results from radioembolization with regards to tumor response and delay of tumor progression.

Fendler et al treated 81 patients with metastatic breast cancer to the liver, with the majority in a single session whole liver approach.[19] While standard RECIST imaging was not used, 52% of the patients demonstrated a significant decrease in the standardized uptake value to PET imaging after treatment. Median overall survival after radioembolization was 8 months.

Pieper et al reported results on 44 patients with metastatic breast cancer to the liver undergoing both glass and resin microsphere radioembolization.[20] This represented an extremely advanced staged population, where 73% of the patients had been already treated with greater than 5 lines of systemic chemotherapy. Most patients had extrahepatic disease at the time of treatment, and most had multifocal or diffuse tumors throughout the liver. Based on RECIST imaging criteria, objective response was achieved in 29% of the patients. Median survival was 6 months after treatment.

While the overall lengths of survival initially appear somewhat limited, all the published series in this population focused on patients who has significant hepatic tumor burden, many with extrahepatic disease, and most had been previously treated with numerous lines of systemic chemotherapy. Without treatment, survival in this patient population is typically poor. Despite the lack of direct comparative studies, these results trend toward higher rates of hepatic toxicity compared to other metastatic malignancies. Given that the baseline hepatic function and performance status are similar, it is likely that the extensive exposure to systemic chemotherapy in this specific population may make the likelihood of hepatic toxicity higher. For example, Pieper reported the onset of ascites in 12 of 44 treated patients within the first 3 months.[20] Despite normal baseline hepatic function with respect to laboratory values, many systemic agents used in metastatic breast cancer may result in some

Table 3 Studies Assessing Effectiveness of ^{90}Y Radioembolization for Ocular Melanoma Metastases

Study	Device	Patients, *n*	Extrahepatic Disease	Prior Treatment	Tumor Burden	Radiologic Response (CR + PR), Criteria Used	Survival (Months)*
Kennedy[15]	Resin	11	NR	NR	100% multifocal	77% RECIST	80% at 1 year
Gonsalves[17]	Resin	32	NR	100%	6% greater than 50% tumor burden	6% RECIST	10.0
Eldredge-Hindy[27]	Resin	71	55%	58%	NR	8% RECIST	12.3
Klingenstein[28]	Resin	13	46%	85%	15% greater than 50% tumor burden	62% RECIST	7.0
Xing[18,†]	Resin	15	NR	100%	31% with greater than 10 tumors	18% RECIST	10.9

CR, complete response; NR, not reported; PR, partial response.
*Survival measured from time of ^{90}Y treatment.
†Only patients with uveal melanoma undergoing radioembolization are listed.

Table 4 Studies Assessing Effectiveness of ^{90}Y Radioembolization for Metastatic Breast Cancer

Study	Device	Patients, *n*	Extrahepatic Disease	Prior Chemotherapy	Tumor Burden	Radiologic Response (CR + PR), Criteria Used	Survival (Months)*
Fendler[19]	Resin	81	67%	100%	10% greater than 50% tumor burden	NR	8.1
Gordon[29]	Glass	75	77%	100%	7% greater than 50% tumor burden	35% RECIST	6.6
Pieper[20]	Glass & resin	44	89%	100%	14% greater than 50% tumor burden	29% RECIST	6.1
Saxena[30]	Resin	40	60%	100%	5% greater than 50% tumor burden	31% RECIST	13.6
Cianni[31]	Resin	52	46%	100%	13% greater than 50% tumor burden	56% RECIST	11.5
Haug[32]	Resin	58	66%	100%	34% greater than 25% tumor burden	26% RECIST	10.8

CR, complete response; NR, not reported; PR, partial response.
*Survival measured from time of ^{90}Y treatment.

degree of subclinical hepatic dysfunction. Once exposed to hepatic arterial therapy such as radioembolization, the hepatic dysfunction may become unmasked. Therefore, it is advised to approach these patients with appropriate counseling, consideration of other treatment options, and a more conservative approach with respect to dosimetry and extent of hepatic tissue perfused in any single setting (Tables 2-4).

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