Transarterial Chemoembolization and Selective Internal Radiation for the Treatment of Patients with Metastatic Neuroendocrine Tumors: A Comparison of Efficacy and Cost

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ABSTRACT

Background. Hepatic arterial therapy (HAT) has been proven to be effective at palliation of hormonal symptoms of metastatic neuroendocrine tumors (NETs), as well as a means of cytoreduction. Recently, the newer modalities of yttrium-90 and drug-eluting beads with doxorubicin (DEBDOX) have been reported to be effective in the treatment of metastatic NETs. The aim of this study was to compare the safety, efficacy, and cost of selective internal radiation with DEB therapy.

Methods. An institutional review board–approved, multicenter, multinational prospective treatment registry to investigate the safety and efficacy of yttrium-90 and doxorubicin microspheres was reviewed.

Results. In all, 43 patients underwent a combined 69 HAT treatments, with 15 patients receiving 23 yttrium-90 treatments and 28 patients receiving 46 DEB-

DOX treatments. The extent of disease—based on the number of lesions, bilobar distribution, patient performance status, and size of largest lesion—was similar in both the yttrium-90 and DEBDOX groups. After a median follow-up of 12 months, response rates were similar with the two treatments, but then there was a significantly lower response rate in the yttrium-90 group at 12 months than in the DEBDOX group. In an evaluation of cost for the two treatments, the median cost for yttrium-90 was \$25,243 and the median cost for DEBDOX was \$13,400.

Conclusion. HAT is a safe and effective therapy in patients with unresectable NETs to the liver. The size of the lesions, total lesion volume, and expense of therapy need to be considered when choosing which HAT method is optimal. *The Oncologist* 2011;16:594–601

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INTRODUCTION

Carcinoid tumors and pancreatic neuroendocrine tumors (NETs) have a predilection for metastasizing to the liver [1]. Unfortunately, these heterogeneous tumors do not come to clinical attention until they have metastasized and are producing mass effects, hormonal effects, or hepatic parenchymal replacement. The presence of liver metastases is associated with a poor prognosis, with a median survival time of 2 years after the diagnosis of hepatic metastases. Unfortunately, <10% of these patients have surgically resectable disease [2].

Systemic cytotoxic chemotherapy has a limited role in the treatment of NETs and is associated with significant toxicity. Carcinoid tumors have demonstrated significant resistance to systemic chemotherapy and pancreatic NETs have modest response rates [3]. A large proportion of these neuroendocrine liver metastases secrete biologically active substrates that cause symptoms that greatly affect quality of life. Somatostatin analogs have been the mainstay in the management of these symptoms, but eventually the disease becomes resistant to these agents.

Liver metastases from NETs are known to be highly hypervascular. This concept led to the use of transarterial hepatic chemoembolization (TACE) as a means of treating this disease with the palliative intent of reducing tumor burden and symptom control. Because of the degree of vascularity of these lesions, response rates have been as high as 70%–90%. Several published reports have demonstrated that TACE can reduce hormonal levels, palliate symptoms, and reduce tumor burden in many patients with hepatic carcinoid metastases [4, 5].

Selective internal radiation therapy containing yttrium-90, a β emitter, is another emerging approach in the treatment of liver metastases and has been shown to be effective and well tolerated in patients with unresectable hepatic metastases [6]. Similarly, drug-eluting beads with doxorubicin (DEBDOX) has also been found to be safe and effective in the management of metastatic NETs to the liver [7].

There are no large-scale reports assessing the efficacy, safety, and cost of these treatment modalities for hepatic metastases from NETs. Thus, the aim of this study is to compare the safety, efficacy, and cost of selective internal radiation with those of DEB therapy.

MATERIALS AND METHODS

An institutional review board–approved prospective, multi-institutional, open, noncontrolled repeat treatment registry of 200 patients undergoing 358 treatments for primary or secondary cancers in the liver was evaluated from January 2007 to October 2008 [8]. Forty-three patients presenting with liver-dominant metastatic carcinoid to the liver were

treated with either yttrium-90 therapy using SIR-Spheres® (SIRTex Medical Limited Sydney, Australia) or TheraSphere® (MDS Nordion, Ottawa, Canada) or DEBDOX (DCBead™/LCBead™; Biocompatibles UK, Surrey, U.K.). The registry was initiated to satisfy the strict criteria for critical appraisal of the quality of a registry study with (a) a well-described patient population, (b) hypothesis-generating and hypothesis-answering questions, (c) high-quality data with good quality control, (d) independent assessment of outcomes, (e) clinically relevant follow-up with minimal loss of patients, and (f) comparable patient evaluation across all institutions participating [8].

Patients were included for therapy as described previously [9]. Standard pretherapy evaluation of patients with metastatic carcinoids included at least a three-phase computed tomography (CT) scan of the abdomen and pelvis and chest roentgenogram at least 1 month prior to treatment. Prior systemic chemotherapy of any type and duration was allowed and was recorded.

Patients were followed for any treatment-related adverse experiences for 30 days after each treatment, and monitored for survival for 2 years. All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0. Follow-up assessments included a three-phase CT scan of the liver within 1–2 months from treatment completion with evaluation of the enhancement pattern of the target lesion and tumor response rates measured according to modified Response Evaluation Criteria in Solid Tumors.

Diagnostic angiography was performed by an interventional radiologist and consisted of selective celiac and superior mesenteric arteriograms to evaluate the hepatic arterial anatomy. The decision to treat with either bead was at the physician's discretion.

DEBDOX treatment was defined by the amount of liver disease, which is integral to determining both the number of treatments performed and the type and position of the catheter. For patients with a finite numbers of lesions (defined as fewer than four), a planned treatment cycle included a minimum of two dosing schedules of 100–150 mg of DEBDOX loaded in two bead vials of either 100–300 μ m, 300–500 μ m, or 500–700 μ m (every 4–8 weeks). Toxicity was followed and the interval was extended if toxicity was seen, with a plan of either two or three treatment cycles based on the extent of liver involvement and with a repeat scan every 3 months from the initial treatment cycle to evaluate response as well as planned retreatment. For diffuse disease, a four-dose schedule was planned with beads of 100–300 μ m and 100–150 mg doxorubicin (depending on the tumor burden and extent of the hepatic parenchyma re-

serve). The plan included at least two treatments per lobe with a 3- to 4-week dosing interval. Toxicity was followed and the interval was extended if toxicity was seen, with a planned repeat CT scan 3 months after the first dose to evaluate tumor response. For example, a patient who presented with bilobar disease would receive the first bead treatment to right lobe, then a second bead treatment to left lobe 3 weeks later, then a third bead treatment to right lobe 3 weeks later, and a fourth bead treatment to the left lobe again 3 weeks later. A change from this plan was dictated both by the patient's tolerance to the therapy and by the degree of hepatic arterial stasis that was encountered following a treatment (e.g., if the left lobe was treated and after 75% of the planned dose there was near complete stasis, then that lobe would not receive another planned treatment).

For yttrium-90 treatment, a pretherapy visceral angiography consisting of 100 MBq of ^{99m}Tc albumin aggregated was administered for assessment of extrahepatic shunting. The presence of significant hepatopulmonary shunting ($>15\%$) constituted a contraindication to this particular therapy. Patients found to be suitable candidates for treatment were administered yttrium-90 in a lobar fashion 10–14 days following the initial assessment. Patients with bilobar disease were treated in two separate treatments, 1 month apart. Follow-up CT imaging was performed 6 weeks after treatment in order to restage and confirm the safety of this therapy. Initial response to treatment was made at 3-month intervals using CT scanning. After each serial scan, a decision on whether or not a particular patient needed another treatment, resection, or observation, or appeared to have received little or no benefit from the procedure was made.

Technical success for either yttrium-90 or DEBDOX was defined as the ability to deliver $\geq 75\%$ of the planned dose of therapy at each treatment.

In an evaluation of reimbursement, cost, and profit profiles for these therapies, all the established Current Procedural Terminology codes were queried, including the complex coding by procedure, vessel-specific coding, and additional supervising and interpreting codes that are billed depending on the location of the catheter within the vasculature. Catheterization codes 36425–36427, 75726, 75774, 37204, 75894, 75898, and others, indicate first- through third-order vessel therapy was included. The Standard Diagnosis Related Group, International Classification of Diseases, 9th Revision, Healthcare Common Procedure Coding System, and Ambulatory Payment Classification were reviewed to compare the reimbursement, cost, and profit profiles of these therapies.

Data were censored at the last recorded patient contact if an endpoint was not reached. Recurrence was defined as ev-

idence of viable tumor by radiologic CT criteria of a vascular mass. In the event of subsequent hepatic therapy for disease recurrence, only the first procedure was used for the purposes of this study. The χ^2 test, Student's *t*-test, and Mann-Whitney *U*-test for nominal, continuous, and ordinal variables, respectively, were used to evaluate the association between independent variables and surgical complications. A proportional hazards analysis was performed on all variables found significant on univariate analysis. Relative risks with 95% confidence intervals were calculated as a measure of association. Differences with a *p*-value $< .05$ were considered significant. The statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC).

RESULTS

All 43 patients were included in this study, with a median age of 59 and a range of 44–87 years (Table 1). None of the patients had received prior systemic chemotherapy. The median number of metastatic lesions among these patients was nine (range, 4–25). Similarly, the median number of target lesions was four (range, 2–5) and 12 patients (47%) had bilobar disease, with the remaining patients having predominantly right lobe disease. The median size of the largest hepatic metastasis was 3.2 cm (range, 2–8.3 cm) and nine patients (20%) had some form of extrahepatic disease, with the most common being bone and lung metastases. In total, 30 patients (70%) had metastatic neuroendocrine symptoms, including at least symptoms of diarrhea, flushing, or rash. Extent of disease based on the number of lesions, bilobar distribution, patient performance status, and the size of the largest lesion was similar in both the yttrium-90 and DEBDOX groups.

In all, 43 patients underwent a combined 69 treatments, with 15 patients (three receiving TheraSphere® and 12 receiving SIR-Spheres®) receiving 23 yttrium-90 treatments and 28 patients receiving 46 DEBDOX treatments (Table 2). The median number of total treatment sessions per patient was 1 with a range of 1–2 (Table 2).

For the DEBDOX treatments, the total planned dose of doxorubicin given per treatment session was a median of 100 mg (range, 75–150 mg). In all, 46 treatments were administered with 100% technical success, including the ability to deliver all planned doses, with a median dose of 100 mg (range, 75–150 mg). The planned dose was at the physician's discretion, but was primarily based on the ability to deliver one vial (maximum, 75-mg dose) or two vials (maximum, 150-mg dose) based on tumor distribution and vascular anatomy. Thirty-eight of the 46 treatment sessions were performed with a lobar approach. The bead sizes were 100–300 μm alone for nine treatments, 100–300 μm com-

Table 1. Clinical characteristics of all low-grade neuroendocrine cancer patients

Characteristics (<i>n</i> = 43)	All patients treated	Yttrium-90 (<i>n</i> = 15)	DEBDOX (<i>n</i> = 28)
Median age (range), yrs	59 (44–87)	57 (44–72)	59 (49–87)
Gender (male/female)	19/24	7/8	12/16
Past medical history			
Cardiac	5	3	2
Vascular	1	1	0
Pulmonary	3	2	1
Diabetes	5	3	2
Insulin	4	2	1
Noninsulin	1	1	1
Alcohol	2	0	2
Tobacco	13	4	9
Median packs	35	25	40
Hypertension	12	6	6
Prior cholecystectomy	7	4	3
Karnofsky performance status score			
100%–90%	36	14	22
80%–70%	7	1	6
Location of primary			
Pancreas	9	4	5
Small bowel–appendix	13	3	10
Unknown	13	3	10
Stomach	2	0	2
Colon	3	3	0
Node	3	2	1
Extent of liver lesions			
Distinct number	14	5	9
Numerous	29	10	19
Liver involvement			
<25%	17	6	11
26%–50%	16	5	11
51%–75%	10	4	6
<i>n</i> of liver tumors			
1	4	0	4
2	3	2	1
≥3	36	13	23
Total <i>n</i> of tumors (size, cm)	16 (1–45)	12 (2–45)	16 (1–30)
Median sum of target lesion(s) size (range), cm	7 (2.3–37.5)	6.2 (2.3–23)	7.9 (4–37.5)
Lesion location			
Right lobe only	9	2	7
Left lobe only	4	1	3
Bilobar	30	12	18

Abbreviation: DEBDOX, drug-eluting beads with doxorubicin.

combined with 300–500 μm for 16 treatments, 300–500 μm alone for 13 treatments, and 300–500 μm combined with 500–700 μm for five treatments. The degree of flow occlusion per treatment session was partial stasis in 15, near sta-

sis in 14, and complete stasis in 13 treatments. The overall length of stay was a median of 23 hours, with a range of 23 hours to 2 days.

For the yttrium-90 therapy, all 23 treatments were administered with 100% technical success. The median dose delivered in the first treatment was 1.23 GBq and the median dose delivered in the second treatment was 1.55 GBq (Table 2). The degree of flow occlusion was near in six and complete in 17 treatments. The overall length of stay in all 23 treatments was outpatient.

In both the yttrium-90 and DEBDOX groups, 10 patients in total sustained 19 adverse events within 30 days of each treatment session (Table 3). Most adverse events were either grade I or grade II toxicity. The most common adverse events that either required a longer stay beyond the 23-hour admission or required the physician to call in additional medication during the recovery period were pain (*n* = 5) and nausea (*n* = 3). Two patients died in the yttrium-90 group—one developed acute femoral arterial thrombosis 2 weeks after therapy and died from multisystem organ failure and the other died from hepatic failure 28 days following the second treatment. The first patient underwent emergent limb revascularization but developed pneumonia following repair and refused intubation and expired, per the patient's wishes. The second patient developed acute hepatic decompensation 28 days after the second treatment, with no evidence of biliary dilation and no other extrahepatic source, and this was felt to be related to the yttrium-90 therapy. The patient was supported and stabilized for a 4-week period of time in the hospital and then was transferred to subacute rehabilitation, where the patient expired 4 weeks later from cardiac arrest. In two patients, hepatic dysfunction developed following yttrium-90 therapy that did not resolve and persisted with medical refractory ascites, which required multiple paracentesis treatments in one patient and peritoneal shunting in the other patient. There were no deaths in the DEBDOX group, but one patient developed grade 3 hepatic dysfunction following the fourth DEBDOX treatment. All other adverse events resolved within 3–4 weeks after each treatment session and none of these adverse events impeded our ability to retreat within the planned treatment schema. All hepatic dysfunction seen in the DEBDOX-treated patients resolved within 35 days after their last treatment.

Follow-Up and Tumor Response

Follow-up data are available for all 43 patients with a median follow-up duration of 12 months and with the normal follow-up schema being within 4–6 months after the first treatment, 9 months, and then 12 months after completion of treatment. In the 30 patients who had symptoms prior to

Table 2. Bead catheter infusion outcomes

	Yttrium-90 (<i>n</i> = 15 patients)	LCBead™ (<i>n</i> = 28 patients)	<i>p</i> -value
<i>n</i> of treatments	23, 2 (1–2)	46, 1 (1–6)	
Technical success	100%	100%	NS
Median dose delivered (range)	1.065 (0.21–2.35)	100 (10–150)	NA
Total hepatic dose exposure	1.46 (0.55–2.01) ^a	150 (10–550) ^b	NA
1	1.23 (0.33–1.9)	120 (10–150)	
2	1.55 (0.55–2.01)	200 (76–350)	
3	–	250 (151–500)	
>3	–	537.5 (525–550)	
Complication rate (%)	9.5%	18%	.08
Extrahepatic infusion	0%	0%	NS
Blood serum changes ^c			
WBC	–0.8 (–11.52 to 4.2)	–0.21 (–9.46 to 9.2)	NS
Hemoglobin	0.35 (–1.2 to 2.1)	0.4 (–5 to 5.8)	NS
Bilirubin	0.1 (–0.2 to 0.4)	0.1 (–0.4 to 8.9)	NS

^aTotal cumulative dose in GBq.^bTotal cumulative dose in mg of doxorubicin.^cTiming of labs was on the day of treatment and at 48 hours posthepatic arterial treatment.

Abbreviations: NA, not applicable; NS, not significant.

Table 3. Bead infusion–related morbidity

Side effect (<i>n</i> = 19)	Yttrium-90		LCBead™		<i>p</i> -value, all grades
	All grades, %	Severe grade, % ^a	All grades, %	Severe grade, % ^a	
Nausea	0%	0%	6.5%	2.2%	0.02
Vomiting	0%	0%	8.7%	6.5%	0.02
Hypertension	0%	0%	0%	0%	NS
Liver dysfunction/failure	7%	7% ^b	2.2%	2.2%	0.18
Anorexia	0%	0%	2.2%	2.2%	0.5
Pain	2%	0%	8.7%	4.3%	0.006
Pancreatitis	0%	0%	0%	0%	NS
Hematological	0%	0%	0%	0%	NS
Bleed	0%	0%	0%	0%	NS
Other embolic event	7%	7% ^b	0%	0%	NS

^aDefined as grade ≥3.^bDefined as death during follow-up treatment.

Abbreviation: NS, not significant.

therapy, 90% had resolution of their symptoms at their 3-month follow-up. After a median follow-up of 12 months, response rates were similar with the two treatments, at 100% at 3 months and 100% and 90% for yttrium-90 and DEBDOX, respectively, at 6 months, but then a significantly lower response rate in the yttrium-90 group at 12 months (46%) than in the DEBDOX group (66%; $p < .05$) (Table 4). The yttrium-90 patients were all salvaged with

DEBDOX and achieved stable disease. In an evaluation of survival, the two treatments were similar, with the DEBDOX group having a longer follow-up time and a significantly longer hepatic-specific progression-free survival duration ($p < .05$) (Table 5). Multivariate predictors of 12-month hepatic-specific failure (i.e., progression of disease) in the yttrium-90 group were target lesions >5 cm in size ($p = .05$), the sum of the target lesion sizes >15 cm ($p =$

Table 4. Hepatic-specific response rate for all patients evaluated

Response	Yttrium-90 (n = 15)					LCBead™ (n = 28, 11 patients)				
	3 mos	6 mos	12 mos	18 mos	24 mos	3 mos	6 mos	12 mos	18 mos	24 mos
Complete response	1	2	2	2	2	0	3	3	7	3
Partial response	14	13	5	10 ^a	6	28	22	17	11	15
Stable disease	0	0	2	1 ^a	0	0	3	1	5	1
Disease progression	0	0	6	0	0	0	0	2	0	1
Follow-up not reached	0	0	0	0	7	0	0	5	5	8
Response rate	100%	100%	46%			100%	90%	72%	66%	66%

^aDefined as patient salvaged with repeat LCBead™ treatment after progression at 12 months.

Table 5. PFS, hepatic-specific survival, and overall survival

Median survival, mos	Yttrium-90	LCBead™
PFS	14	18
Hepatic	12	28
Extrahepatic	15	16
Overall survival		
From diagnosis	28	69
From first treatment	17.7	25

Abbreviation: PFS, progression-free survival.

.02), and the inability to deliver >120 Gy ($p = .01$) to the planned lobe.

In an evaluation of reimbursement, cost, and profit at both the local Louisville Medical Center and the U.S. national level for both methods, there was a significantly higher product cost, reimbursement, hospital cost, hospital profit, and physician reimbursement with yttrium-90 therapy (Table 6). The Louisville *median cost for each treatment* for yttrium-90 was \$25,243 (range, \$22,227–\$40,478) and for DEBDOX delivered via LCBead™ was \$13,400 (range \$8,283–\$16,198) ($p = .0001$).

DISCUSSION

Metastatic NETs to the liver present a growing therapeutic challenge because of their resistance to systemic and biologic therapies. These tumors have a mixed-biology growth pattern, with some being slow growing and others exhibiting a more aggressive growth pattern, similar to small cell-type cancers. The diagnosis is varied because, typically, patients are not brought to clinical attention until hormonal or mass effect symptoms appear as a result of progression of disease. According to the Surveillance, Epidemiology, and End Results database, the incidence and prevalence of this disease have increased significantly over the last few decades. The overall incidence is 2.5–5 per 100,000. Surgical

resection is the primary therapy for carcinoid liver metastases, when indicated. The indication for resection is a multifactorial decision process, based on the biology of the tumor; timing of metastasis; size, location, and number of metastases; presence or absence of extrahepatic disease; and performance status of the patient. Because hepatic metastases are responsible for most of the morbidity and mortality in this disease, liver-directed therapies yield great benefit as therapies for those in whom resection is not an option.

Hepatic arterial therapy (HAT) in the management of metastatic carcinoid has a demonstrated response rate as high as 70%–90%, as a result of the fact that these lesions are hypervascular. The HAT modalities previously reported to be used against this disease include chemoembolization, bland embolization, and selective internal radiation (yttrium-90 microspheres) (Table 7) [10–16]. The rationale for this therapy is the fact that primary and secondary hepatic tumors derive their blood supply from the hepatic artery, whereas approximately 50% of the oxygen supply to the normal liver is from the portal system. Experiments have demonstrated that chemotherapy given through the hepatic artery achieved a 10 times higher intratumoral concentration than when delivered via the portal vein.

The literature is lacking in large-scale controlled trials using HAT for carcinoid metastases, simply based on the large variation in disease presentation from the size, number, and location of tumors; presence of extrahepatic disease; patient performance status; and referral bias. The existing literature consists mainly of many single-center reports with a small number of patients. Schell et al. [15] studied 24 patients with metastatic carcinoid treated with hepatic arterial chemoembolization—19 patients demonstrated a decrease in tumor size and four others achieved stable disease. A majority (64%) of the patients became asymptomatic and 46% were able to discontinue octreotide.

Table 6. The median Louisville and national reported economics of reimbursement, cost, and profit for drug-eluting bead therapy compared with yttrium-90 therapy

Product procedure	Product cost (1 treatment)	Median local Louisville economics	Median national reported economics						Median physician reimbursement
			Outpatient			Inpatient			
			Reimbursement	Cost	Profit	Reimbursement	Cost	Profit	
CAM Protocol C TACE	\$200	\$11,895	\$11,242	\$1,898	\$9,344	\$9,194	\$3,898	\$5,206	\$2,153
LCBead™ TACE	\$3,190	\$13,400	\$11,222	\$4,847	\$6,375	\$9,104	\$6,847	\$2,257	\$2,153
Yttrium-90	\$13,000	\$25,243	\$34,683	\$18,218	\$16,465	\$27,731	\$19,218	\$8,513	\$4,169
Abbreviations: CAM, cisplatin, adriamycin, mitomycin; TACE, transarterial hepatic chemoembolization.									

Table 7. Previous reports of hepatic arterial therapies in metastatic neuroendocrine tumors

Study, therapy	n	Symptoms	Mortality	Morbidity	Improve symptoms	Overall survival (median)
Pitt et al. [10], TACE	100	100%	1.8%	6.5%	88%	25.7 mos
Brown et al. [11], Bland	78	85%	0	13%	95%	PFS, 9 mos
de Baere et al. [12], DEBDOX	20	85%	0	22%	NR	PFS, 15 mos
Rhee et al. [13], yttrium-90	42	NR	0	13%	NR	26 mos
Kennedy et al. [14], yttrium-90	148	NR	0	6.5%	NR	70 mos
Schell et al. [15], bland	24	85%	0	NR	64%	5-yr, 53.5%
Bloomston et al. [16], TACE	122	85%	5%	23%	92%	33.3 mos

Abbreviations: DEBDOX, drug-eluting beads with doxorubicin; NR, not reported; PFS, progression-free survival; TACE, transarterial hepatic chemoembolization.

Pitt et al. [10] evaluated 100 patients using conventional TACE, demonstrating acceptable morbidity and mortality and an 88% improvement in symptoms, with a fairly reasonable and well-established median overall survival time in patients who were not eligible for more aggressive resection or ablative therapy. Brown et al. [11] reported, in 1999, their initial use of bland embolization for NETs. The report was recently updated as an Abstract at the World Conference of Interventional Oncology, showing again the use of bland embolics with improvement in symptoms; however, the hepatic-specific, progression-free survival duration was only 9 months. The report demonstrated that bland embolization is an effective modality; however, it is not a durable modality in the long term. de Baere et al. [12] presented an initial review of 20 patients undergoing DEBDOX-based therapy with no mortality and a slightly higher rate of morbidity, but a longer hepatic-specific, progression-free survival time of 15 months. The two largest yttrium-90 reports, from Rhee et al. [13] and Kennedy et al. [14], again showed minimal morbidity but a vast difference in terms of the median overall survival time. The multi-institutional study from Rhee et al. [13] demonstrated a median overall survival time of 26 months; however, the multi-institutional review from Kennedy et al. [14] showed a dramatically longer

median overall survival time of 70 months, thus confirming the dramatic heterogeneous nature that some patients present and the wide range in median overall survival times that exists in this patient subset, sometimes regardless of the HAT used. Bloomston et al. [16] presented the single largest series using conventional TACE, demonstrating a median overall survival time similar to that of previous reports, and also finding dramatic improvements in symptoms. Most importantly, Bloomston et al. [16] provided a cautionary statement related to the 5% mortality rate that was seen in this review. Thus, the review confirmed that, even if HAT is easy to perform because of its percutaneous access, there still remains a risk for overall mortality because of the dramatic response rates that can be seen in a subset of patients with large, bulky disease with >50% liver involvement.

These studies, outlined in Table 7, all demonstrate the effectiveness of HAT for improving symptoms and with some improvement in the median overall survival time. At the present time, HAT delivering an agent appears to have the more durable hepatic-specific, progression-free survival advantage when compared with bland embolization. However, given the ever-increasing awareness of health care economics, the overall expense of these therapies can-

not be downplayed (Table 6). In our trial, patients receiving either DEBDOX or yttrium-90 had similar initial response rates. The DEBDOX group experience a slightly higher incidence of adverse effects but a more durable hepatic-specific response. These therapies are fairly equivalent in terms of overall outcome, with a trend toward a more durable outcome overall with DEBDOX-based treatment. In addition to the greater durability of response, one of the more dramatic differences is in terms of the overall costs of these two treatments. Currently, a yttrium-90 treatment is nearly three times the cost of a DEBDOX-based treatment and, given the fact that the majority of patients need at least two yttrium-90 treatments, the cost-to-durable-response ratio becomes dramatic when you compare it with that of other HATs or DEBDOX-based treatment. Similarly, the hepatic-specific toxicity cost should continue to be evaluated. As presented in our results, the hepatic toxicity of this therapy can present 9–12 months after a complete response, with a clinical presentation of uncontrolled cirrhosis with ascites, failure to thrive, and hypoalbuminemia that is difficult to control. Awareness of these long-term side effects is essential in order to effectively choose which therapy is optimal, not just in the short term but also in the long term, given the long overall survival duration that can be achieved in these patients.

This review, in combination with the results of other reviews, continues to demand that a more hepatic-specific distribution be developed to definite conditions under

which these various treatment options can be the most effective. The presented results do confirm the effectiveness of yttrium-90, but its effect is in the small, 1.0- to 2.0-cm, lesion that has a miliary bilobar distribution, which leads to a more dramatic long-term response rate. In comparison, patients who have more bulky, large (>5.0 cm in size) lesions need to be treated with a more segmental targeted approach for which DEBDOX-based treatment is potentially more advantageous. Future reviews and, more importantly, future studies, must present long-term follow-up as we as categorize the lesion size, lesion distribution, and lesion percentage of liver involvement in order to truly define the optimal treatment for this heterogeneous patient population.

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AUTHOR CONTRIBUTIONS

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