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REVIEW

Effects of Yttrium-90 selective internal radiation therapy on non-conventional liver tumors

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Abstract

The liver is a common site of metastasis, with essentially all metastatic malignancies having been known to spread to the liver. Nearly half of all patients with extrahepatic primary cancer have hepatic metastases. The severe prognostic implications of hepatic metastases have made surgical resection an important first line treatment in management. However, limitations such as the presence of extrahepatic spread or poor functional hepatic reserve exclude the majority of patients as surgical candidates, leaving chemotherapy and locoregional therapies as next best options. Selective internal radiation therapy (SIRT) is a form of catheter-based locoregional cancer treatment modality for unresectable tumors, involving trans-arterial injection of microspheres embedded with a radio-isotope Yttrium-90. The therapeutic radiation dose is selectively delivered as the microspheres permanently embed themselves within the tumor vascular bed. Use of SIRT has been conventionally aimed at treating primary hepatic tumors (hepatocellular carcinoma) or colorectal and neuroendocrine metastases. Numerous reviews are available for these tumor types. However, little is known or reviewed on non-colorectal or non-neuroendocrine primaries. Therefore, the aim of this paper is to systematically review the current literature to evaluate the effects of Yttrium-90 radioembolization on non-conventional liver tumors including those secondary to breast cancer, cholangiocarcinoma, ocular and percutaneous melanoma, pancreatic cancer, renal cell carcinoma, and lung cancer.

Key words: Liver metastases; Breast cancer; Melanoma; Cholangiocarcinoma; Radioembolization; Selective internal radiation therapy; Selective internal radiation therapy; Transarterial radioembolization; Transarterial radioembolization; Yttrium-90

Core tip: Selective internal radiotherapy or transarterial radioembolization with Yttrium-90 microspheres is a targeted catheter-based therapy indicated for unresectable metastatic liver tumors. A number of reviews and meta-analyses have been written on the use of Yttrium-90 in the treatment of liver metastases, however few broadly investigate results from non-colorectal or non-neuroendocrine primaries. Our objective is to consolidate the current literature to better delineate the response and survival outcomes of Yttrium-90 radioembolization on non-conventional liver tumors including breast cancer, cholangiocarcinoma, ocular and percutaneous melanoma, pancreatic cancer, renal cell carcinoma and lung cancer.

INTRODUCTION

In the United States and Europe, metastases to the liver are forty times more common than primary liver tumors[1]. Nearly half of patients in the United States with extrahepatic primary cancer have hepatic metastasis[1]. The prevalence of metastatic liver disease is attributed physiologically to dual blood supplies to the liver and the easily penetrable nature of the fenestrated endothelium lining of the hepatic sinusoids[2].

Essentially all metastatic malignancies have been known to metastasize to the liver, with carcinomas being histologically most common, followed by lymphomas and sarcomas. Primary sites by frequency include upper gastrointestinal including stomach, pancreas, and gallbladder (44%-78%), colon (56%-58%), breast (52%-53%), lung (42%-43%), esophagus (30%-32%), genitourinary organs (24%-38%)[1].

Metastatic liver disease frequently originates from the gastrointestinal tract *via* the portal venous drainage. Another known but less common route of metastasis is through systemic arterial circulation. Lymphatic spread and peritoneal fluid extension is less common[1].

Surgical resection is the first line treatment of all liver metastasis, however the majority (over 75%) of patients are excluded as surgical candidates, leaving chemotherapy and locoregional therapies as the next best option[3]. Traditional contraindications to resection include extrahepatic disease, unfitness for surgery, and extensive liver involvement limiting the ability to leave adequate hepatic functional reserve[4].

Isolated liver metastases amenable to local therapy are more commonly associated with colorectal cancer, with 20%-30% of metastatic colon cancers being confined to the liver[5,6]. Most other tumors including gastric cancer, pancreatic cancer, breast cancer, lung cancer, neuroendocrine tumors, and melanoma commonly present with systemic, disseminated disease[7]. Numerous studies in the past on surgical resection of liver metastases have achieved improved survivability with colorectal and neuroendocrine primaries over other tumor types[8-11]. As such, the prognostic opportunity for colorectal and neuroendocrine liver metastases has attracted a majority of research in regional therapies for the treatment of unresectable disease. The role of regional therapy in treating non-conventional liver metastases remains less studied and more controversial.

Selective internal radiotherapy (SIRT) or transarterial radioembolization (TARE) with Yttrium-90 microspheres is a targeted catheter-based therapy indicated for unresectable metastatic liver tumors. Its efficacy is centralized on two principles: (1) that hepatic tumors source over 90% of their blood supply from the hepatic artery; and (2) that tumor neovascularity is denser than the surrounding parenchyma[12]. During the procedure Yttrium-90 microspheres are trans-arterially infused into the liver. The beads penetrate and permanently embed themselves within the tumor vascular bed, selectively delivering the therapeutic radiation dose over two weeks[13-18].

Currently, Yttrium-90 microsphere products are commercially available in either glass (TheraSphere) or resin (SIR-Spheres). Therasphere is US Food and Drug Administration (FDA) approved under a Humanitarian Device Exemption in 1999 as radiation treatment or neoadjuvant to surgery for unresectable hepatocellular carcinoma. SIR-Spheres have received FDA approval in 2002 for unresectable metastatic colorectal cancer. Yttrium-90 radioembolization has also had documented off-label use in the treatment of metastatic liver disease with other known primaries. A number of reviews and meta-analyses have been written on the use of Yttrium-90 in the treatment of liver metastases, however few broadly investigate results from non-colorectal or non-neuroendocrine primaries[6,12,19-29]. Our objective is to consolidate the current literature to better delineate the response and survival outcomes of Yttrium-90 radioembolization on non-conventional liver tumors.

LITERATURE RESEARCH

A systematic literature search was conducted using PubMed, EMBASE, and Cochrane Library for "Yttrium-90" and "Y90" as well as synonyms for "radioembolization" and "liver metastasis." A total of 28 studies containing non-conventional primaries undergoing Yttrium-90 radioembolization were included for review. Studies providing only unified results for multiple primary tumors were excluded. Of the studies with results distinguished by primary tumor, 10 studies contained

breast, 6 contained melanoma, 8 contained cholang-iocaricnoma, 3 contained pancreatic, 2 contained renal cell carcinoma, and 3 contained lung or thoracic[30-50].

BREAST CANCER

Breast cancer is the most commonly diagnosed cancer in women, expected to account for 29% of all new cancers diagnosed among women[51]. Breast cancer confined to the primary site has a promising prognosis, with estimated 5-year survival rates exceeding 99%[51]. Overall survival has continued to steadily improve with risk of death decreasing 1%-2% annually[34,51]. The outlook significantly worsens for the estimated 20%-30% of patients who develop distant metastatic disease, with 5-year survival rates as low as 16%-25%[51-53]. Surveillance, Epidemiology, and End Results (SEER) data from the National Cancer Institute collected between 1973 and 1995 estimate cumulative survival with metastatic breast cancer at time of diagnosis is estimated at 18.5 mo[54]. Median survival in patients with unresectable, chemoresistant breast cancer liver metastases (BRCLM) ranges between 3-10 mo[55]. The majority of patients with fatal metastatic breast cancer (up to 60%) die of liver failure caused by hepatic metastasis[35,56,57].

Clinical management for breast cancer liver metastases has predominantly involved systemic chemotherapy over surgical resection for a multitude of reasons. First, effective chemotherapy has long been established before other metastatic tumor types such as colorectal cancer, where surgical resection was considered the first-line treatment early on. Second, liver metastases are considered an ominous sign of poor outcome relative to other metastatic sites[58]. Third, solitary liver metastases are rare in the setting of breast cancer (< 5%). Less than 20% of patients qualify as surgical candidates[58-60]. As a result, it is imperative that alternative therapies for patients with unresectable, chemoresistant BRCLM to be investigated. Among the therapies available are transarterial chemoembolization, transarterial radioembolization or SIRT, radiofrequency ablation, and stereotactic therapy.

Of the studies on SIRT of non-conventional liver metastases, breast cancer is the most studied (Table 1). So far we found 7 exclusively BRCLM SIRT studies[31,33,35,39,47,48,50] in addition to 3 mixed primary studies that provide discrete response data on the patients with breast primaries[34,45,46].

The first study investigating survival of BRCLM patients undergoing SIRT was in 2007 by Bangash *et al*[31] who assessed 27 patients with progressing liver metastases on polychemotherapy. Of the 23 patients who made it to the 90-d follow-up computed tomography (CT) scan, 39.1% showed either complete or partial response by WHO criteria. 63% of all 27 patients showed positive tumor response on PET. Median survival for the 21 patients with tumor burden < 25% and 6 patients with tumor burden > 25% were 9.4 and 2.0 mo, respectively. The authors concluded that although the tumor response with SIRT was encouraging, the influence on survival remained unclear.

A larger study in 2007 by Coldwell *et al*[35] included a total of 44 women with unresectable chemorefractory BRCLM. On 12-wk follow-up CT, 47% of 36 patients had a partial response by RECIST criteria. 95% of all 44 patients showed a response on PET scan. The patients had not met their median survivability at 14 mo, however 86% of patients were alive at that time. Patients non-responsive by CT or PET scan had a median survival of 3.6 mo. Based on an expected median survival of patients with advanced breast cancer responding to standard chemotherapy of 14 mo, the authors predicted the patients would demonstrate an increase in overall survival.

In 2008, Jakobs *et al*[39] followed 30 unresectable chemorefractory BRCLM patients undergoing SIRT. Follow-up data available for 24 patients revealed a 61% partial response rate by RECIST criteria. Survivability in patients with no response correlated closely to Coldwell *et al*[35] at 5.7 mo *vs* 3.6 mo. The median overall survival of 11.7 mo corresponds closely to the 9.4 mo survival in patients with < 25% tumor burden in Bangash *et al*[31] considering the majority (23/30) of patients fell under that criteria.

In 2013, the largest study to date reported SIRT of 77 unresectable chemorefractory BRCLM patients. Response rates were consistent with prior studies with a partial response rate of 56% by RECIST criteria. Median survival of 11.5 mo was nearly identical to that reported by Jakobs *et al*[39]. In patients ECOG 0, with < 25% tumor burden and no extrahepatic disease, median survival was promising at 14.3 mo[33].

Later that year, Saxena *et al*[47] reported their experience with 40 patients affected by unresectable, chemoresistant BRCLM. Response rates were lower than prior studies at 31% overall, however complete response was observed in 5% of patients. Conversely, median survival was slightly higher than prior studies at 13.6 mo.

In 2014, Gordon *et al*[50] studied 75 patients with progressive chemorefractory breast cancer liver metastasis and stable extrahepatic disease reports a significantly lower median OS of 6.6 mo. The patient cohort consisted of over 40% of patients with tumor burden greater or equal to 25%, which is proportionally higher than the tumor burdens reported in other studies mentioned above. Partial response and stable disease was reported in 35.3% and 63.2% of patients respectively.

In summary, multiple studies have demonstrated Yttrium-90 SIRT as an effective procedure for unresectable chemoresistant BRCLM. Collective analysis of current literature ranges response rates between 18%-61% and median overall survival between 6.6 to 13.6 mo. Though response rates and

Table 1 Breast cancer studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage or activity)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Gordon *et al*[50] (8/2014 Epub, RS)	Therasphere (mean 1.52 Gbq)	Breast (75)	RECIST and PET @ 1.4 mo (median)	RECIST 24 (35.3) PR 43 (63.2) SD 1 (1.5) PD 7 lost PET 3 (12) CR 18 (72) PR or SD 4 (16) PD 50 lost	6.6 mo
Seyal *et al*[48] (8/2014, RS)	Unspecified (no dosage info)	Breast (21) 34 lesions	RECIST 1.1 @ unspecified	34 lesions 6 (17.7) PR 27 (79.4) SD 1 (2.9) PD	None
Saxena *et al*[47] (12/2013, RS)	SIR-Spheres (mean 1.67 Gbq)	Breast (40)	RECIST @ 1 mo	2 (5) CR 10 (26) PR 15 (39) SD 11 (29) PD 2 lost	13.6 mo
Cianni *et al*[33] (1/2013, RS)	SIR-Spheres (median 1.9 Gbq)	Breast (77)	RECIST and PET @ 1.8 mo	29 (56) PR 18 (35) SD 5 (10) PD 25 ineligible	11.5 mo
Jakobs *et al*[39] (5/2008, PC)	SIR-Spheres (mean 1.9 Gbq)	Breast (30)	RECIST @ 4.2 mo (median)	14 (61) PR 8 (35) SD 1 (4) PD 7 lost	11.7 mo (all) 23.6 mo (responders) 5.7 mo (nonresponders)
Coldwell *et al*[35] (3/2007, RS)	SIR-Spheres (median 2.1 Gbq)	Breast (44)	RECIST and PET @ 2.8 mo	RECIST 17 (47) PR 17 (47) SD 2 PD (5) PD 8 lost PET scans 42 (95) response 2 (5) no response/progression	Median OS not reached 86% 14-mo survival
Bangash *et al*[31] (5/2007, PC)	Therasphere (median 1.70 Gbq, mean 2.05 Gbq)	Breast (27)	WHO and PET @ 3 mo	WHO 9 (39.1) CR/PR 12 (52.1) SD 2 (8.8) PD 4 lost PET 17 (63) response 10 (37) no response	Median OS not given. 6.8 mo (ECOG 0) 2.6 mo (ECOG 1,2,3) 9.4 mo (< 25% tumor burden) 2.0 mo (> 25% tumor burden)
Cianni *et al*[34] (1/2010, RS)	SIR-Spheres (mean 1.64 Gbq)	Breast (32, data extracted from larger study)	RECIST @ 1.8 mo	14 (44) CR/PR 11 (34) SD 7 (22) PD	None
Reiner *et al*[46] (1/2014, PC)	SIR-Spheres (mean 1.5 Gbq)	Breast (1, data extracted from larger study)	RECIST 1.1 @ 4 mo	1 (100) CR/PR	None
Pöpperl *et al*[45] (4/2005, PC)	SIR-Spheres (mean 2.27 Gbq)	Breast (4, data extracted from larger study)	PET @ 3 mo	3 (100) Regression 1 lost	None

PC: Prospective cohort study; RS: Retrospective study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival; OR: Overall response.

survival outcomes vary significantly depending on selection criteria, they are generally improved over past controls. Breast cancer metastasis are often uniformly hypervascular and slow growing, which based on previous studies with colorectal carcinoma and neuroendocrine tumors make it an ideal target for SIRT[35,61,62]. BRCLMs also typically present numerous and widespread, placing limitations on what other therapies such as stereotactic radiotherapy or conventional chemoembolization can achieve while maintaining adequate liver function. Still, the tendency of BRCLM to present with extrahepatic involvement limits SIRT from a prognostic perspective. Although the number of studies on the effects of SIRT on breast cancer metastasis is gradually increasing, they have so far involved only relatively small, heterogenous patient cohorts. In order to validate SIRT as a potential first-line adjuvant to chemotherapy, larger multicenter randomized control studies are needed. The potentially synergistic relationship with post-treatment chemotherapy also warrants further investigation and careful consideration in select patients[47].

CHOLANGIOCARCINOMA

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after hepatocellular carcinoma. Incidence of ICC has been on the rise[63,64]. Median overall survival of patients for ICC patients is currently 22 mo. Untreated, median survival with ICC is significantly lower at 3-8 mo[65]. Curative resection is the mainstay of therapy in ICC, however few qualify mostly due to advanced hepatic disease. ICC is rapidly fatal for those with unresectable disease, though improvements in non-operative therapy have brought median survival in unresectable disease to 15 mo *vs* 6 mo before the year 2000[66]. Treatment has traditionally involved systemic chemotherapy agents 5-flourouracil and leukovorin[67]. Newer palliative agents like floxuridine and gemcitabine as well as liver directed techniques like hepatic arterial infusion, transarterial chemoembolization, and transarterial radioembolization have been selectively implemented in the past decade.

ICC has recently accumulated a small body of studies dedicated toward liver directed treatment with yttrium-90 SIRT (Table 2). Our literature search found 8 ICC-only SIRT studies, mostly published within the past two years (2013-2014). A systematic review and meta-analysis by Boehm *et al*[63] draws conclusions from 5 of these studies[3,68-71]. In the meta-analysis, the highest median overall survival was with hepatic arterial infusion (22.8 mo) compared to transarterial radioembolization (13.9 mo), transarterial chemoembolization (12.4 mo), and drug-eluting transarterial chemoembolization (12.3 mo). The authors point out the results should be interpreted with caution due to potential selection bias.

Not included in the analysis by Boehm *et al* are three more recent studies[72-74]. The first study by Mouli *et al*[74] expands on the pilot study by Ibrahim *et al*[69], adding 22 patients to the previous cohort. In the study, 25% of patients exhibited partial response by WHO criteria. Overall survival varied significantly between solitary (14.6 mo) and multifocal (5.7 mo) lesions[74]. The second study by Camacho *et al*[72] on 21 chemorefractory ICC patients reports a median survival of 16.3 mo. The last study by Filippi *et al*[73] on 18 ICC patients reports an 82.5% response rate by PET scan and a median overall survival of 14.8 mo. Survivability data from the 3 most recent reports are consistent with the 13.9 mo overall survival by meta-analysis reported by Beohm *et al*[63].

Yttrium-90 SIRT is considered at some centers a preferred first-line therapy for low-tumor burden ICC[74]. Reasons for this include the benefit of being able to downstage previously unresectable ICC for curative resection. Though median overall survival data is shorter than that of hepatic arterial infusion, Yttrium-90 therapy carries fewer risks including not having to implant a chemoinfusion port.

OCULAR AND CUTANEOUS MELANOMA

Melanoma is a less common yet particularly lethal form of skin cancer, accounting for 75% of skin cancer related deaths. The most common types of melanoma are cutaneous (over 90%) and ocular (around 5%)[75,76]. Unlike most other cancer types, the incidence of cutaneous melanoma is on the rise[51]. Though ocular and cutaneous melanomas both arise from melanocytes, they have distinct patterns of disease progression. Ocular (uveal) melanomas have a tendency to metastasize to the liver (occurring in 95% of metastatic disease), whereas liver metastasis occurs in just 15%-20% of metastatic cutaneous melanomas. With either type of melanoma, liver metastasis is attributed to a grim prognosis and is often the cause of death[77,78]. Reported median overall survival is 2.4 mo with liver involvement, 7.2 mo with non-visceral metastases, and 11.4 mo with lung metastases[79]. As a first-line treatment, standard chemotherapy has been traditionally ineffective, though new research has shown improved survival with vemurafenib and new immunotherapies like ipilimumab[80,81]. For those with chemorefractory liver metastases, liver directed therapy is a preferred approach to reduce tumor burden and prolong overall survival. Surgical resection is not a viable option for the majority (91%) of patients based on extensive hepatic or extra-hepatic involvement[37]. Transcatheter therapy *via* transarterial infusion (TAI) chemotherapy and transarterial chemoembolization have had reported favorable response rates and improved clinical outcomes in those with unresectable liver metastases[49].

In addition, four studies have been done on yttrium-90 SIRT of melanoma liver metastases (Table 3). The first study in 2009 by Kennedy *et al*[40] on 11

Table 2 Cholangiocarcinoma studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage or activity)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Ibrahim *et al*[69] (10/2008, PC)	Therasphere (median 105.1 Gy)	ICC (24)	WHO @ 1 mo	6 (27) PR 15 (68) SD 1 (5) PD 2 lost	14.9 mo 31.8 mo (solitary) 6.1 mo (extrahepatic disease)
Saxena *et al*[71] (2/2010, PC)	SIR-Spheres (mean 1.76 Gbq)	ICC (25)	RECIST @ 8.1 mo (median)	6 (26) PR 11 (48) SD 5 (22) PD 2 lost	9.3 mo
Haug *et al*[68] (6/2011, PC)	SIR-Spheres (no dosage info)	ICC (26)	RECIST @ 2.8 mo	5 (22) PR 15 (65) SD 3 (13) PD 3 lost	11.7 mo
Hoffmann *et al*[3] (2/2012, RS)	SIR-Spheres (median 1.54 Gbq)	ICC (33)	RECIST @ 3 mo	12 (36) PR 17 (52) SD 4 (12) PD	22 mo
Rafi *et al*[70] (4/2013, PC)	SIR-Spheres (mean 1.20 Gbq)	ICC (19)	RECIST @ 3 mo	2 (11) PR 13 (68) SD 4 (21) PD	11.5 mo
Mouli *et al*[74] (8/2013, PC)	Therasphere (no dose info)	ICC (46) Note: overlaps with Ibrahim *et al*	WHO @ 1 mo	11 (25) PR 33 (73) SD 1 (2) PD	No median OS 14.6 mo (solitary) 5.7 mo (multifocal)
Camacho *et al*[72] (2/2014, PC)	SIR-Spheres (no dose info)	ICC (21)	RECIST mRECIST EASL @ 1 mo	RECIST 1 (4.7) PR 16 (76.2) SD 4 (19.1) PD mRECIST 13 (62.0) PR 4 (19.0) SD 4 (19.0) PD EASL 2 (9.5) PR 15 (71.4) SD 4 (19.1) PD	16.3 mo
Filippi *et al*[73] (8/2014, PC)	SIR-Spheres (not given)	ICC (18)	PERCIST @ unspecified	14 (82.3) PR 3 (17.6) SD	14.8 mo

ICC: Intrahepatic cholangiocarcinoma; PC: Prospective cohort study; RS: Retrospective study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival; OR: Overall response.

uveal melanoma patients reported a strikingly high response rate of 77% with a 1-year survival of 80%. One patient that failed 13 prior bland embolization procedures had complete response after one radio-embolization treatment.

In 2011, Gonsalves *et al*[37] studied a larger cohort consisting of 32 patients with hepatic metastasis of uveal melanoma. In contrast to the prior study by Kennedy *et al*[40] just 6% had treatment response by RECIST criteria. Median overall survival was 10.0 mo. The low response rate was attributed to the inclusion of salvage patients with bulky, treatment resistant progressive lesions and high tumor burden (7 patients above 25% hepatic tumor burden). Of note, median radiation treatment activity in the study by Gonsalves *et al*[37] was 1.08 Gbq *vs* 1.55 Gbq in Kennedy *et al*[40].

In 2014, Memon *et al*[42] published a mixed mela-noma type study consisting of 7 ocular, 4 cutaneous, 3 rectal and 2 unknown melanomas. Response to

therapy was 31% by RECIST criteria. Median overall survival was short at 7.6 mo, attributed to high tumor burden (56% of patients had > 25% tumor burden) and the presence of extrahepatic disease (63%) at presentation. The authors conclude that further investigations are needed to rationalize radioembolization over other forms of locoregional therapies.

Later that year, Xing *et al*[49] published a slightly larger mixed melanoma type study consisting of 15 ocular and 13 cutaneous melanomas compared to a supportive care group of 30 patients. Two patients suffered yttrium-90 SIRT related mortality in the study. Though imaging response by RECIST criteria was comparable to prior studies at 21% (5/24 patients at follow up), median overall survival was relatively longer at 10.1 mo from time of SIRT therapy. Median overall survival between cutaneous and uveal metastatic melanoma is reported to be similar. The

Table 3 Melanoma studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Xing *et al*[49] (8/2014, RS)	SIR-Spheres (mean 1.86 Gbq)	Melanoma (28) 13 cutaneous 15 ocular	RECIST 1.1 @ 0.9-1.4 mo	5/28 (21) PR 9/28 (38) SD 10/28 (42) PD 4 lost	10.1 mo
Memon *et al*[42] (6/2014, RS)	Therasphere (median 1.87 Gbq)	Melanoma (16) 7 ocular 3 rectal 4 cutaneous 2 unknown	WHO, RECIST, and EASL @ 0.9 mo	WHO 5 (31) CR/PR 8 (50) SD 3 (19) PD RECIST 5 (31) CR/PR 8 (50) SD 3 (19) PD EASL 6 (38) CR/PR 7 (43) SD 3 (19) PD	7.6 mo
Gonsalves *et al*[37] (2/2011, RS)	SIR-Spheres (median 1.08 Gbq)	Ocular melanoma (32)	RECIST 1.0 @ 1 mo	1 (3) CR 1 (3) PR 18 (56) SD 12 (38) PD	10.0 mo
Kennedy *et al*[40] (7/2009, RS)	SIR-Spheres (median 1.55 Gbq)	Ocular melanoma (11)	RECIST @ 1.4 mo	1 (11) CR 6 (66) PR 1 (11) SD 1 (11) PD 2 lost	Median OS not reached
Reiner *et al*[46] (1/2014, PC)	SIR-Spheres (mean 1.5 Gbq)	Melanoma (2, data extracted from larger study)	RECIST 1.1 @ 4 mo	1 (50) CR/PR 1 (50) SD/PD	None
Lim *et al*[41] (4/2005, PC)	SIR-Spheres (no dosage info)	Ocular melanoma (1, data extracted from larger study)	RECIST @ 2 mo	1 (100) PD	None

PC: Prospective cohort study; RS: Retrospective study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival; OR: Overall response.

authors mentioned that the 19.9 mo median overall survival from time of hepatic metastases compares favorably over prior metastatic melanoma studies with other forms of treatment including systemic chemotherapy (12.0 mo), transarterial infusion (14.0 mo), transarterial chemoembolization (9.03 mo).

Given the hypervascular and aggressive nature of melanoma liver metastases, locoregional treatment with SIRT appears to be a reasonable approach at reducing disease progression. Median overall survival ranges from 7.6 to 10.1 mo, substantially improved over the expected less than 3 mo reported decades ago[79]. As with many other tumor types, patients undergoing SIRT with less hepatic involvement and the absence of extrahepatic disease tend to achieve better survival rates. Based on the few small cohort studies so far, SIRT has been demonstrated to be safe and effective at prolonging survival, however without further comparative studies the ideal selection criteria and benefit over other regional therapies remains uncertain.

PANCREATIC CANCER

Metastatic pancreatic cancer carries a notoriously dismal prognosis[82]. Systemic chemotherapy centralized around Gemcitabine, the current mainstay of treatment, brings median overall survival to around 5-7 mo[83-85]. Initial reports with advanced pancreatic cancer using the novel chemotherapy regimen FOLFIRINOX introduced in 2010 documented a median overall survival of 11.1 mo, the most significant improvement in survival seen thus far[86]. Among the treatment options specific to pancreatic cancer liver metastases, surgical resection of liver disease at the time of pancreatic resection has had high complication rates and poor long-term outcomes[87-90]. Alternative locoregional therapies such as Yttrium 90 SIRT have been investigated as adjuncts for the purpose of slowing disease progression.

A paucity of clinical data exists on Yttrium-90 SIRT for liver metastases of pancreatic cancer patients (Table 4). So far just 2 small cohort, single center studies

Table 4 Pancreatic cancer studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage or activity)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Michl *et al*[43] (12/2013, RS)	SIR-Spheres (1.0-2.5 Gbq)	Pancreatic (19)	RECIST @ 2.6 mo (median)	9/13 (64.3) PR 4/13 (35.7) PD 6 lost	9 mo
Cao *et al*[32] (11/2010, RS)	SIR-Spheres (no dosage info)	Pancreatic (7)	RECIST @ 1-2 mo	2 (40) PR 1 (20) SD 2 (40) PD 2 lost	No median OS 1 patient survived to 15 mo
Pöpperl *et al*[45] (4/2005, PC)	SIR-Spheres (mean 2.27 Gbq)	Pancreatic (1, data extracted from larger study)	PET @ 3 mo	1 (100) Regression	None

PC: Prospective cohort study; RS: Retrospective study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival; OR: Overall response.

have been published. The first small study in 2010 by Cao *et al*[32] included 7 pancreatic adenocarcinoma patients with liver metastases. 2 patients died prior to initial follow up. Two (40%) of the remaining 5 exhibited partial response by RECIST criteria. Average median survival is not provided, but the authors report that one patient survived nearly 15 mo after SIRT therapy[32]. A second, slightly larger study in 2014 by Michl *et al*[43] on 19 chemorefractory pancreatic patients with metastatic liver disease reports an encouraging median overall survival of 9.0 mo. 5 patients died and 1 patient was omitted for disease progression prior to initial follow up. Of the 13 patients at initial follow up, 64.3% exhibited partial response by RECIST criteria. 9 patients received adjuvant chemotherapy after surgery. The authors also found a correlation with serum markers CA 19-9 and CRP and shorter overall survival.

Though the limited available data makes survivability benefits unclear, initial reports as a salvage treatment are encouraging. Median survival with the small cohort is attributed to a roughly 2-4 mo improvement over conventional gemcitabine combination therapy alone, however improvement over the new chemotherapy regimen FOLFIRINOX has yet to be demonstrated. Response rates by RECIST criteria are consistent with established response rates with colorectal and neuroendocrine metastatic liver disease. Further studies are needed to delineate the proper patient selection criteria for optimal patient outcome.

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is currently responsible for 2%-3% of malignancies in the US. Incidence of RCC in the U.S. is on the rise, with an estimated over 63000 new cases and over 13000 deaths are expected in 2014[51]. Cumulative 5-year survival rates for all US RCC patients have improved from 50% in 1975-1977 to 73% in 2003-2009[51]. With the advent of newer targeted therapies including anti-VEGF and m-TOR targeted agents, median overall survival has more than doubled to greater than 2 years[91]. Approximately 33%-50% of patients with renal cell carcinoma eventually develop metastatic disease[92,93]. Metastatic RCC is frequently unresponsive to external beam radiotherapy, high-dose IL-2 and systemic chemotherapy[93]. The most common site of metastases is the lung (45%-75%). Metastatic disease to the liver affects 20%-40% of patients, and the overwhelming majority (over 96%) are accompanied by widespread disease[93-96]. Patients with hepatic involvement have a reported median overall survival of 7.4 mo[97]. Though few patients qualify, the relatively uncommon procedure of surgical resection of hepatic metastases has shown promising survival outcomes at the cost of significant morbidity and mortality risks. Two-year overall survival for metastatic renal cell carcinoma with and without hepatectomy has been reported at 40% and 10%, respectively[93]. Experience with locoregional therapies like SIRT in the treatment of renal cell carcinoma liver metastases is very limited (Table 5).

The pilot study for yttrium-90 SIRT of chemorefractory renal cell carcinoma liver metastases was in 2012 by Abdelmaksoud *et al*[30] Median overall survival for 6 patients was 12 mo. Of the 5 patients that made it to initial follow-up, 3 (60%) had complete response and 1 (20%) had partial response by RECIST criteria. Two patients died within 2 mo of treatment from unrelated extra-hepatic causes. A case report published in 2013 by Hamoui *et al*[38] on a 76-year-old woman with metastatic sarcomatoid renal cell carcinoma undergoing palliative SIRT was done on both a left renal tumor and the right hepatic lobe. CT scan at 8 wk and 3 mo both showed stability of the renal cell carcinoma and hepatic metastases. At past 9 mo, the patient subsequently developed worsening metastatic disease and died 23 mo after radioembolization.

Like neuroendocrine tumors, the hypervascular nature of renal cell carcinoma makes for an attractive target for treatment of liver metastasis with SIRT[98]. Additionally, patients with numerous metastatic foci

Table 5 Renal cell carcinoma studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage or activity)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Abdelmaksoud *et al*[30] (3/2012, RS)	SIR-Spheres (median 1.89 Gbq)	RCC (6)	mRECIST @ 25 mo (mean)	3 CR (60) 1 PR (20) 1 PD (20) 1 lost	12 mo
Hamoui *et al*[38] (2/2013, case report)	Therasphere (80 Gy)	RCC (1)	Unspecified @ 1.8 mo	1 (100) SD	Patient died 23 mo after SIRT

SIRT: Selective internal radiation therapy; RS: Retrospective study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival.

Table 6 Lung or thoracic cancer studies *n* (%)

Author (publish date and study type)	Type of microsphere (average dosage or activity)	Type of mets (patients)	Response criteria @ 1st assessment	Response	Median OS
Gaba *et al*[36] (8/2012, case report)	Therasphere (1.57-3 Gbq)	Squamous cell lung cancer (2)	PET CT @ 2-3 mo	2 (100) CR	Patient 1: Alive 11 mo after SIRT Patient 2: Alive 2 mo after SIRT
Murthy *et al*[44] (2/2008, RS)	SIR-Spheres (no dosage info)	Lung cancer (6) 2 carcinoids 3 adenocarcinomas 1 small cell carcinoma	Unspecified @ unspecified	1 (17) PR 1 (17) "minor response" 1 (17) SD 3 (50) PD	2.7 mo
Reiner *et al*[46] (1/2014, PC)	SIR-Spheres (mean 1.5 Gbq)	NSCLC (1, data extracted from larger study)	RECIST 1.1 @ 4 mo	1 (100) CR/PR	None

SIRT: Selective internal radiation therapy; RS: Retrospective study; PC: Prospective cohort study; CR: Complete response; PR: Progressive response; PD: Progressive disease; SD: Stable disease; OS: Overall survival.

difficult to treat by ablation and stereotactic techniques may be better off with treatment *via* transarterial infusion. Post-operative pain with SIRT is expected to be less than other embolization procedures like chemoembolization and bland embolization because SIRT doesn't cause large vessel occlusion[38]. In the treatment of liver metastasis from renal cell carcinoma, SIRT is limited by the rarity of liver-dominant metastases and the known resistance to radiation[30]. However, based preliminary data on a handful of patients, initial reports are promising for the use of SIRT of hepatic metastases by renal cell carcinoma with a palliative rather than curative intent.

LUNG CANCER

Lung cancer is the leading cause of cancer death, with an estimated over 159000 lung cancer related deaths expected in 2014. At stage Ⅳ, non-small cell lung cancer and small cell lung cancer have a combined 4% chance of 5-survival[51]. Treatment of stage Ⅳ lung cancer is especially challenging and consists of predominantly palliative chemotherapy[99]. Surgical resection of liver metastases in the setting of metastatic lung cancer has been traditionally considered not worthwhile[100,101], though it has been

performed successfully in select patients[102].

The value of yttrium-90 SIRT of lung cancer has been seldom looked into and the available data is extremely limited (Table 6). In 2008, Murthy *et al*[44] published a retrospective analysis of 6 patients with various lung cancers. Included were 3 adenocarcinomas, 2 carcinoids, and 1 small cell carcinoma. It is reported that 2 patients had partial response, 1 patient had stable disease, and 3 patients developed progressive disease. Median overall survival was 2.7 mo from radioembolization to death. A case report published in 2012 by Gaba *et al*[36] presents complete response after SIRT of liver metastases in two chemorefractory squamous cell lung cancer patients. At the time of the study, both patients were alive at 11 mo and 2 mo following SIRT therapy.

The poor response to systemic chemotherapy and dismal survival rates with metastatic lung cancer emphasizes the need to further study alternative therapies. The few cases of yttrium-90 SIRT of lung cancer liver metastases so far demonstrate SIRT's potential as an effective salvage therapy. In lung cancer especially, clinicians must be mindful of non-target radiation to the lungs due to potentially limited baseline pulmonary function. With further studies, the criteria in which SIRT becomes a worthwhile therapy in

metastatic lung cancer can be better defined.

CONCLUSION

Although the indications for Yttrium-90 SIRT in nonconventional liver metastases are less well-defined, initial results of small studies are largely favorable. Overarching limitations include marked cohort heterogeneity, the absence of a gold standard in response criteria, and variations in treatment dosing. Disparities in median overall survival amongst tumor types may be explained by small cohort size and variations in tumor burden, progressiveness, time to first follow up, and presence of extra-hepatic disease. These studies demonstrate that whether or not Yttrium-90 SIRT provides a justifiable benefit to any given patient relies tremendously on both tumor type and patient status. With larger, multi-centered randomized controlled studies, established clinical guidelines can develop that ultimately improve patient outcomes.

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