

Review

Yttrium-90 Microspheres: A Review of Its Emerging Clinical Indications

Natthida Khajornjiraphan^a Nyein Aye Thu^a
Pierce Kah Hoe Chow^{b,c,d}

^aDepartment of General Surgery, Singapore General Hospital, ^bDepartment of Surgical Oncology, National Cancer Centre, ^cDepartment of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital, ^dOffice of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

Key Words

Cancer · Emerging indications · Treatment · Yttrium-90

Abstract

Background: Many patients with liver malignancies are not candidates for resection, and systemic therapies are often not effective. Radioembolization (RE) is an alternative treatment for this group of patients. The safety and efficacy of RE with yttrium 90 (Y90) in patients with hepatocellular carcinoma (HCC) or metastatic colon cancer to the liver have been proven in several studies. However, fewer studies have focussed on the safety and efficacy of RE with Y90 in other extrahepatic primary and secondary liver cancers. The effect on outcomes of concomitant use of Y90 with a systemic therapy is still currently under investigation. **Summary:** A review of the published data on the use of RE as stand-alone, concomitant or sequential with other treatment modalities in HCC and other primary and secondary liver cancer is reported here. **Key message:** RE for the treatment of HCC and other extrahepatic, primary and secondary liver cancer has reasonable efficacy and acceptable toxicities. Definitive studies to establish the role of RE in the treatment of such malignancies are warranted.

Copyright © 2014 S. Karger AG, Basel

Background

HCC is the third most common cause of cancer related mortality worldwide where approximately 650,000 people die from it each year [1, 2]. Curative treatments that offer high rates of complete response (CR) for early HCC are surgical resection, transplantation and

Pierce Kah Hoe Chow, MBBS, M.Med, FRCS, FAMS, PhD

Office of Clinical Sciences, Duke-NUS Graduate Medical School,
The Academia, Level 6, 20 College Road, 169856 (Singapore)
Tel. +65 6576 7845, E-Mail pierce.chow@duke-nus.edu.sg

radiofrequency ablation (RFA) [3–6]. Other therapies that have been shown to improve survival are transarterial chemoembolization (TACE) [7] and sorafenib [8, 9]. Radioembolization (RE) with yttrium 90 (Y90) is an emerging therapy for which good overall survival (OS) has been reported in selected patients with intermediate to advanced stage HCC [10]. To the best of our knowledge, there have been no randomised studies reported for Y90 in HCC, although a number of trials are ongoing [11, 12].

Y90 is a pure beta emitter with a 2.6-day half-life and an average tissue penetration of 2.5 mm in liver and in recent years, it has been used in RE [which is also known as selective intra-arterial radiotherapy (SIRT)] [13]. Two companies are currently engaged in the commercial production and distribution of Y90-labelled microspheres. TheraSphere[®], produced by BTG International (London), was approved by the Food and Drug Administration (FDA) in 1999 for the treatment of unresectable HCC, whereas SIR-Spheres[®] by Sirtex Medical (Sydney), was approved by the FDA in 2002 [14]. In the Asia-Pacific region, Australia and Europe, SIR-Spheres are indicated for the treatment of patients with unresectable liver cancer. In the United States, SIR-Spheres with adjuvant inter-hepatic artery floxuridine chemotherapy are indicated for the treatment of unresectable metastatic liver tumours from primary colorectal cancer [15].

RE for primary and secondary liver cancers involves the infusion of Y90-labelled microspheres directly to the tumour(s) via a hepatic artery catheter. The Y90-labelled microspheres are preferentially taken up by hypervascular hepatic tumours such as HCC, which derive 80–100% of their blood flow from the hepatic arterial system [14, 16]. Clinical usages of RE have expanded from the treatment of primary and secondary liver cancers to the treatment of extrahepatic tumours [14, 17]. RE has been used both as monotherapy as well as in combination with systemic agents such as sorafenib, it has also been used to downstage liver tumours for more definitive procedures such as transplantation, resection or RFA [12, 18]. A number of reports detailing the use of RE from a variety of clinical trials and experiential settings have demonstrated the safety and efficacy of RE in the treatment of HCC, metastatic colorectal cancers and neuroendocrine tumours (NETs) [19–21]. In this article, we review recent data on RE in the treatment of other primary liver cancers, extrahepatic cancers and metastatic liver cancers as well as the concomitant and sequential usages of RE with other treatment modalities.

Methods

A literature review of the PubMed database was conducted for studies published in English from 1994 to 2014 analysing the outcomes of RE in primary and secondary liver cancers. The key words “Yttrium 90,” “radioembolization,” “selective internal radiotherapy,” “primary liver cancers” and “secondary liver cancers metastases” were used in the search for relevant studies that utilized RE.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) reports on treatment with RE written in English; (2) clinical studies; (3) report outcomes that include OS, progression-free survival (PFS), objective response to treatment and toxicities; and (4) the provision of clear documentation of the studies. Exclusion criteria were (1) articles not written in English, (2) letters, editorials, expert opinions and technical notes and (3) non-human studies.

Outcomes of Interest and Complications

The primary outcome elucidated was OS. Secondary outcomes included tumour response (TR), progressive disease (PD) and toxicities.

Primary Liver Cancers Other than HCC

Cholangiocarcinoma

Although the current standard of care for intrahepatic cholangiocarcinomas (ICCs) is resection, ICCs are frequently diagnosed at an advanced stage not amenable to resection [22, 23]. Several locoregional therapies such as RFA, TACE and RE have been used for the treatment of ICC. Treatment with RFA is reported to have high recurrence rates, with low efficacy for tumours larger than 5cm [24]. Retrospective studies on TACE demonstrated survival benefits and tolerable toxicity. RE has also been reported in the treatment of ICCs, published data from five studies reporting the treatment with RE of unresectable ICCs showed median OS ranging from 9.3 to 22 months (table 1) [25–30]. Survival benefits were reported to be highly dependent on the baseline tumour and patient characteristics [31]. Reported toxicities included fatigue, self-limiting abdominal pain, grade 3 hyper-bilirubinemia, grade 3 alkaline phosphatase toxicity, treatment-related gastroduodenal ulcers, grade 3 thrombocytopenia, transient abdominal pain, vomiting, anorexia and nausea [26–30]. These five studies suggested that RE is potentially efficacious and safe for the treatment of ICCs.

Sarcoma

Primary hepatic sarcoma is rare and difficult to treat [32, 33]. No other treatments have been shown to be comparable to surgical resection [34]. One study reported the use of RE in the treatment of primary hepatic sarcoma in 11 patients (table 1) [35]. The median OS was reported to be 8.7 months, with PR or CR of 72.7% and the most commonly reported toxicities were grade 1 fatigue and grade 1 abdominal pain [35].

Secondary Liver Cancers other than from Colorectal Cancers

Metastases from Breast Cancer

Breast cancer is one of the leading causes of death worldwide, with approximately 5–20% of breast cancer patients eventually developing liver metastases [36]. Regardless of there being treatment options such as chemotherapeutic and hormone receptor-based therapies for breast cancer metastases to the liver (BRCLM), the treatment of choice for breast cancer still remains a dilemma. Four studies reported the median OS of BRCLM after RE ranging from 11.5 months to 14.2 months (table 1). Mild to moderate post-embolization syndrome of nausea, vomiting, fever and mild right upper quadrant pain occurred in almost all patients whereas severe toxicities like grade 1 to 3 gastrointestinal toxicities, stomach ulcers and severe hepatic failure were rare [36–39].

Metastases from Cervical Cancer

Although carcinoma of the cervix is one of the most common malignancies among women, metastases to the liver are rare [40]. Metastatic disease or recurrent lesions that are not amenable to local excision or regional radiation have poor prognosis and are often treated with palliative chemotherapy [41, 42]. The prognosis of patients with cervical cancer metastasizing to the liver is poor, with a median survival of 10 months [43].

There are few reports on the use of RE in the treatment of liver metastasis from cervical cancer. A case report detailed the use of pre-operative chemotherapy and RE on a 53-year-old woman who had a history of cervical cancer and developed liver metastasis [44]. RE was administered twice which successfully downsized the hepatic lesion before the patient underwent further treatment with surgical resection.

Table 1. Summary of studies reviewed

Study	Study design	Number of subjects	Median overall survival (months)	Toxicities
Primary liver cancers				
Cholangiocarcinoma				
Saxena et al. (2010) [26]	Prospective	25	9.3	Fatigue (64%) Self-limiting abdominal pain (40%) Grade 3 bilirubin toxicities Grade 3 alkaline phosphatase toxicities (4%)
Ibrahim et al. (2008) [30]	Prospective	24	14.9	Grade 3 albumin toxicities (17%) Grade 3 bilirubin toxicities (4%) Fatigue (75%) Transient abdominal pain (38%) Vomiting (3%) Anorexia (8%) Nausea (4%) Gastroduodenal ulcer (4%) Ascites (14%) Pleural effusion (9%)
Rafi et al. (2013) [27]	Retrospective	19	11.5	Grade 3 thrombocytopenia (5%) Fatigue (21%) Transient abdominal pain (32%)
Hoffman et al. (2012) [28]	Retrospective	33	22	Abdominal pain (84.8%) Nausea (60.6%) Vomiting (27.3%)
Haug et al. (2011) [29]	Retrospective	26	12.8	Transient abdominal pain (58%) Nausea (50%) Vomiting (19%) Duodenal ulcer (8%) Ascites (26%)
Sarcoma				
Oh et al. (2013) [35]	Prospective	11	8.7	Fatigue (54.5%) Abdominal pain (36.4%)
Secondary liver cancer other than from colorectal cancer				
Liver metastasis from breast cancers				
Saxena et al. (2013) [36]	Prospective	77	11.5	Nausea (40%) Vomiting (25%) Self-limiting abdominal pain (20%) Fatigue (15%) Anorexia (5%) Gallbladder and biliary-tree-related complications (5%) Shortness of breath (3%) Ascites (3%) Pleural effusion (3%) Pulmonary embolus (3%)

Table 1. (continue) Summary of studies reviewed

Study	Study design	Number of subjects	Median overall survival (months)	Toxicities
Jakobs et al. (2012) [38]	Prospective	30	14.2	Mild to moderate right upper quadrant pain (87%) Grade 1 or 2 nausea (67%) Grade 3 nausea (3%) Grade 1 vomiting (9%) Grade 2 vomiting (9%) Grade 3 vomiting (3%) Actinic gastric ulcers (6%) Lower leg oedema (6%) Grade 3 toxicity with increasing transaminase levels (3%) Grade 1–2 toxicity with increasing aspartate aminotransferase and alanine aminotransferase levels (87%) Grade 3 toxicities with increasing aspartate aminotransferase and alanine aminotransferase levels (6%)
Coldwell et al. (2012) [37]	Prospective	44	14	Mild abdominal pain (13%) Nausea (13%) Grade 2 cholecystitis (4%) Grade 1 cholecystitis (6%) Grade 2 gastritis (4%) Grade 3 gastritis (4%) Severe hepatic failure (4%)
Cianni et al. (2013) [39]	Retrospective	77	11.5	Nausea (100%) Vomiting (100%) Fever (100%) Mild right upper quadrant pain (100%) Grade 3 gastrointestinal I toxicity (10%) Stomach ulcers (2%)
Metastases from cervical cancer				
Gulec et al. (2009) [44]	Case report	1	Not reported	Mild elevation in alkaline phosphatase
Metastases from pancreatic cancer				
Michi et al. (2014) [46]	Retrospective	19	9	Fever (100%) Nausea (100%) Vomiting (0%) Fatigue (100%) Abdominal pain (100%) Gastric ulceration (7.1%) Liver abscesses (14.1%) Cholangitis (7.1%) Ascites (21.4%) Spleen infarction (7.1%) Radiation-induced liver disease (14.1%)
Cao et al. (2010) [45]	Pilot	7	Not reported	Nausea Fatigue Abdominal pain

Table 1. (continue) Summary of studies reviewed

Study	Study design	Number of subjects	Median overall survival (months)	Toxicities
Metastases from lung cancer				
Murthy et al. (2008) [49]	Prospective	6	2.7	Chest pain (6%) Worsening of pre-existing abdominal discomfort (6%)
Gaba et al. (2012) [50]	Case report	2	5.5	No toxicity mentioned
Extrahepatic cancers				
Lung malignancies				
Ricke et al. (2013) [51]	Case Report	2	6	No serious toxicity reported
Y90 concomitant or in sequential with systemic therapy				
Sharma et al. (2012) [52]	Phase I study	20	9.3 (Reported progression free survival)	Grade 3 abdominal pain 25% Microsphere-induced gastric ulcers 10% Grade 3 and 4 neutropenia 60% Hepatotoxicity 5%
Chow et al. (2014) [12]	Phase II study	29	20.3 (BCLC B) 8.6 (BCLC C)	≥ Grade 1 Toxicities (97%) ≥ Grade 3 Toxicities (52%)
NCT01556490 [55]	Phase III study	Currently Recruiting	Ongoing	Ongoing
NCT01126645 [11]	Phase II study	Currently Recruiting	Ongoing	Ongoing
NCT01135056 [56]	Phase III	Currently Recruiting	Ongoing	Ongoing

In this patient, no extrahepatic disease developed and the tumour was reported to be significantly reduced in size by 25% after the first RE, and further reduced to 10% of pre-treatment size after the second RE [44].

Metastases from Pancreatic Cancer

Hepatic recurrence from pancreatic cancer occurs in more than two-thirds of patients, accounting for one of the major causes of treatment failure in pancreatic cancer [45]. In addition to the current interdisciplinary approach that includes surgery, chemotherapy, radiation therapy and local therapeutic methods, RE has also demonstrated feasibility as a form of liver-directed therapy in cases of hepatic metastases from pancreatic cancer [46].

Published data from two studies showed median OS of 9.0 months (range 0.9–53.0 months); and partial response (PR) in 60% of patients which was related to the baseline levels of carbohydrate antigen 19–9 and C-reactive protein (table 1) [45, 46]. In addition to

short-term toxicities such as nausea, fatigue and abdominal pain, long-term toxicities such as ascites (21.4%) and liver abscesses (14.1%) were reported [46].

Metastases from Lung Cancer

Hepatic metastases complicate approximately 6% of lung cancer cases at the time of diagnosis, and occur in up to 36% of patients over the course of the disease [47]. Current treatments for lung cancer metastasizing to the liver include chemotherapy and/or molecular targeted therapies and rarely, surgery [48]. Although RE is an emerging treatment for lung cancer that metastasizes to the liver, only few studies have focussed on the use of it. In a prospective study, OS of 2.7 months (range: 1–26 months) was reported for the treatment with RE on lung cancer metastasizing to the liver [49]. In a retrospective case study, disease-free survival ranged from 2 to 11 months was reported [50]. Reported toxicities included chest pain in 6% of the patients and worsening of pre-existing abdominal discomfort in another 6%.

Extrahepatic Cancers

Lung Malignancies

Therapeutic alternatives to chemotherapy are few in patients with lung metastases. A case report detailed the delivery of Y90-labelled microspheres via bronchial arteries in two patients [51]. The first patient was a 45-year-old woman with lung metastases from colorectal cancer who had PD following previous treatment with combination chemotherapy of leucovorin calcium, fluorouracil and oxaliplatin (FOLFOX), and surgical resection. The second patient was a 69-year-old man with lung metastasis from renal cell carcinoma who had undergone systemic treatment with sunitinib and sorafenib. He had PD with sunitinib and had severe side effects from sorafenib. Both patients were reported to have undergone successful RE of the lung lesions. The delivery of radioactive Y90-labelled microspheres to the lung was technically feasible and resulted in a reasonable absorbed dose in the tumours. Follow-up computed tomography for both patients showed partial remission of the lesions with no signs of lung pneumonitis or functional impairment.

Y90 Microspheres in Concomitant or in Sequential with Systemic Therapy

Emerging data indicate synergy between RE and systemic chemotherapy for liver tumour metastasizing from colorectal cancers and HCC [52–54]. A phase I study reported combination of RE with radio-sensitizing chemotherapy (oxaliplatin) for treatment of liver metastases from colorectal cancer in 20 patients [52]. PR was noted in 18 patients, SD in two patients and CR in one patient. Overall, result showed that combined RE with radio-sensitizing chemotherapy with oxaliplatin is well tolerated [52].

Besides reports on concomitant treatments, there have also been completed and on-going HCC clinical trials on the sequential treatment of RE followed by systemic therapy [12]. Published data from open-labelled, single arm trial which assessed the safety and efficacy of sequential treatment of RE followed by sorafenib for the treatment of HCC reported median OS being 20.3 and 8.6 month respectively for Barcelona Clinic Liver Cancer (BCLC) stage B and BCLC stage C patient [12]. The study provided evidence that there is potential efficacy and manageable toxicities of sequential treatment with RE and sorafenib [12].

On top of clinical trials on concomitant treatment and sequential treatments, there are on-going clinical trials which compare mono-therapy against combination therapy. One such

trial is a phase 3 trial currently recruiting patients from the United States, Canada and France. It evaluated the safety and effectiveness of Therasphere® in combination with sorafenib against the standard of care sorafenib alone in patients with unresectable HCC [55].

There are also trials comparing RE with other treatment modalities such as RFA and systemic therapy [11, 56]. An on-going phase two study randomized patient with HCC into two treatment arms, RFA followed by sorafenib or placebo against RE with sorafenib or sorafenib alone. This study aimed to evaluate sorafenib and local microtherapy [11]. Yet, another on-going phase three open-labelled randomized controlled trial currently recruiting patient with locally advanced HCC aimed to assess the overall survival between patients receiving RE against those receiving systemic therapy with sorafenib [56].

Discussion and Conclusion

Although RE has been widely used in the treatment of HCC and liver cancer metastases from colorectal cancer and NETs, there is much less data on its application in other primary and secondary liver cancers [48].

While some reports showed enhancement of outcome when RE is used in combination with other treatment modalities, there is no strong evidence. The result of on-going trial may support the benefit of RE in combination with other treatment modalities.

In this review, we summarised relevant reports on the use of RE for treatment of ICC, sarcoma and liver metastases from cervical cancer, pancreatic cancer, breast cancer and lung cancer, as well as for the treatment of primary lung malignancy. While reasonable OS has been reported for treatment with RE, there were also reported toxicities, some of which were serious, e.g., severe hepatic failure. There is a paucity of data from prospective studies: the majority of the published studies we reviewed were retrospective. A significant limitation is that the studies were rather heterogeneous in terms of patient demographics and study designs.

Overall, available data suggest that RE is potentially beneficial for patients with liver malignancies. Prospective studies are required to establish the precise role of RE in the armamentarium of therapies for liver cancers.

References

- 1 Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma: Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. *J Gastroenterol Hepatol* 2010;25:657–663.
- 2 Hung H: Treatment modalities for hepatocellular carcinoma. *Curr Cancer Drug Targets* 2005;5:131–138.
- 3 Belghiti J, Fuks D: Liver resection and transplantation in hepatocellular carcinoma. *Liver Cancer* 2012;1:71–82.
- 4 Mise Y, Sakamoto Y, Ishizawa T, Kaneko J, Aoki T, Hasegawa K, Sugawara Y, Kokudo N: A worldwide survey of the current daily practice in liver surgery. *Liver Cancer* 2013;2:55–66.
- 5 Cheah YL, Chow PK: Liver transplantation for hepatocellular carcinoma: an appraisal of current controversies. *Liver Cancer* 2012;1:183–189.
- 6 Lin SM: Local ablation for hepatocellular carcinoma in Taiwan. *Liver Cancer* 2013;2:73–83.
- 7 Lencioni R: Chemoembolization in patients with hepatocellular carcinoma. *Liver Cancer* 2012;1:41–50.
- 8 Forner A, Llovet JM, Bruix J: Hepatocellular carcinoma. *Lancet* 2012;379:1245–1255.
- 9 Kudo M: Treatment of advanced hepatocellular carcinoma with emphasis on hepatic arterial infusion chemotherapy and molecular targeted therapy. *Liver Cancer* 2012;1:62–70.
- 10 Sangro B, Salem R, Kennedy A, Coldwell D, Wasan H: Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. *Am J Clin Oncol* 2011;34:422–431.
- 11 ClinicalTrials.gov: *Sorafenib and Micro-therapy Guided by Primovist Enhanced MRI in Patients With Inoperable Liver Cancer (SORAMIC)*. 2014 [cited 2014; Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01126645?term=soramic&rank=1>.

- 12 Chow PK, Poon DY, Khin MW, Singh H, Han HS, Goh AS, Choo SP, Lai HK, Lo RH, Tay KH, Lim TG, Gandhi M, Tan SB, Soo KC, Asia-Pacific Hepatocellular Carcinoma Trials Group: Multicenter phase II study of sequential radioembolization-sorafenib therapy for inoperable hepatocellular carcinoma. *PLoS ONE* 2014;9:e90909.
- 13 Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, Bilbao JI, Rodriguez-Fraile M, Rodriguez J, Benito A, Dominguez I, D'Avola D, Herrero JI, Quiroga J, Prieto J, Sangro B: Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology* 2013;57:1078–1087.
- 14 Lewandowski RJ, Geschwind JF, Liapi E, Salem R: Transcatheter intraarterial therapies: rationale and overview. *Radiology* 2011;259:641–657.
- 15 SIRTEX: *Approved Indication*. About SIR-Spheres microspheres 2014 [cited 2014 14/03/2014]; Available from: <http://www.sirtex.com/us/clinicians/about-sir-spheres-microspheres/approved-indication/>.
- 16 Bester L, Meteling B, Pocock N, Saxena A, Chua TC, Morris DL: Radioembolisation with Yttrium-90 microspheres: an effective treatment modality for unresectable liver metastases. *J Med Imaging Radiat Oncol* 2013;57:72–80.
- 17 Bester L, Feitelson S, Milner B, Chua TC, Morris DL: Impact of prior hepatectomy on the safety and efficacy of radioembolization with yttrium-90 microspheres for patients with unresectable liver tumors. *Am J Clin Oncol* 2013;37(5):454–60.
- 18 Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, Hunter RD, Nemcek AA Jr, Abecassis MM, Haines KG 3rd, Salem R: Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006;94:572–586.
- 19 Gulec SA, Pennington K, Wheeler J, Barot TC, Suthar RR, Hall M, Schwartzentruber D: Yttrium-90 microsphere-selective internal radiation therapy with chemotherapy (chemo-SIRT) for colorectal cancer liver metastases: an in vivo double-arm-controlled phase II trial. *Am J Clin Oncol* 2013;36:455–460.
- 20 Saxena A, Chua TC, Bester L, Kokandi A, Morris DL: Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases. *Ann Surg* 2010;251:910–916.
- 21 Lau WY, Leung WT, Ho S, Leung NW, Chan M, Lin J, Metreweli C, Johnson P, Li AK: Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. *Br J Cancer* 1994;70:994–999.
- 22 Razumilava, N. and G.J. Gores, *Cholangiocarcinoma*. *Lancet*, 2014.
- 23 DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD: Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755–762.
- 24 Kim JH, Won HJ, Shin YM, Kim KA, Kim PN: Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. *AJR Am J Roentgenol* 2011;196:205–209.
- 25 Kuhlmann JB, Euringer W, Spangenberg HC, Breidert M, Blum HE, Harder J, Fischer R: Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol* 2012;24:437–443.
- 26 Saxena A, Bester L, Chua TC, Chu FC, Morris DL: Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol* 2010;17:484–491.
- 27 Rafi S, Piduru SM, El-Rayes B, Kauh JS, Kooby DA, Sarmiento JM, Kim HS: Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol* 2013;36:440–448.
- 28 Hoffmann RT, Paprottka PM, Schön A, Bamberg F, Haug A, Dürr EM, Rauch B, Trumm CT, Jakobs TF, Helmburger TK, Reiser MF, Kolligs FT: Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol* 2012;35:105–116.
- 29 Haug AR, Heinemann V, Bruns CJ, Hoffmann R, Jakobs T, Bartenstein P, Hacker M: 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. *Eur J Nucl Med Mol Imaging* 2011;38:1037–1045.
- 30 Ibrahim SM, Mulcahy MF, Lewandowski RJ, Sato KT, Ryu RK, Masterson EJ, Newman SB, Benson A 3rd, Omary RA, Salem R: Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer* 2008;113:2119–2128.
- 31 Turkmen C, Ucar A, Poyanli A, Vatankulu B, Ozkan G, Basaran M, Serin K, Sanli Y, Adalet I: Initial outcome after selective intraarterial radionuclide therapy with yttrium-90 microspheres as salvage therapy for unresectable metastatic liver disease. *Cancer Biother Radiopharm* 2013;28:534–540.
- 32 el-Domeiri AA, Huvos AG, Goldsmith HS, Foote FW Jr: Primary malignant tumors of the liver. *Cancer* 1971;27:7–11.
- 33 Weitz J, Klimstra DS, Cymes K, Jarnagin WR, D'Angelica M, La Quaglia MP, Fong Y, Brennan MF, Blumgart LH, Dematteo RP: Management of primary liver sarcomas. *Cancer* 2007;109:1391–1396.
- 34 Matthaei H, Krieg A, Schmelzle M, Boelke E, Poremba C, Rogiers X, Knoefel WT, Peiper M: Long-term survival after surgery for primary hepatic sarcoma in adults. *Arch Surg* 2009;144:339–344, discussion 344.
- 35 Oh JC, et al: Y-90 radioembolization of primary and metastatic soft tissue sarcomas of the liver. *J Vasc Interv Radiol* 2013;24(Suppl):S148 Abs.342.
- 36 Saxena A, Kapoor J, Meteling B, Morris DL, Bester L: Yttrium-90 radioembolization for unresectable, chemoresistant breast cancer liver metastases: a large single-center experience of 40 patients. *Ann Surg Oncol* 2014;21:1296–1303.

- 37 Coldwell D, Sangro B, Salem R, Wasan H, Kennedy A: Radioembolization in the treatment of unresectable liver tumors: experience across a range of primary cancers. *Am J Clin Oncol* 2012;35:167–177.
- 38 Jakobs TF, Hoffmann RT, Fischer T, Stemmler HJ, Tatsch K, La Fougere C, Murthy R, Reiser MF, Helmberger TK: Radioembolization in patients with hepatic metastases from breast cancer. *J Vasc Interv Radiol* 2008;19:683–690.
- 39 Cianni R, Pelle G, Notarianni E, Saltarelli A, Rabuffi P, Bagni O, Filippi L, Cortesi E: Radioembolisation with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. *Eur Radiol* 2013;23:182–189.
- 40 Guy J, Kelley RK, Roberts J, Kerlan R, Yao F, Terrault N: Multidisciplinary management of hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2012;10:354–362.
- 41 Bujold A, Dawson LA: Stereotactic radiation therapy and selective internal radiation therapy for hepatocellular carcinoma. *Cancer Radiother* 2011;15:54–63.
- 42 Kao YH, Steinberg JD, Tay YS, Lim GK, Yan J, Townsend DW, Budgeon CA, Boucek JA, Francis RJ, Cheo TS, Burgmans MC, Irani FG, Lo RH, Tay KH, Tan BS, Chow PK, Satchithanatham S, Tan AE, Ng DC, Goh AS: Post-radioembolization yttrium-90 PET/CT - part 2: dose-response and tumor predictive dosimetry for resin microspheres. *EJNMMI Res* 2013;3:57.
- 43 Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, Rose SC, Soulen MC, Geschwind JF, Kulik L, Kim YH, Spreafico C, Maccauro M, Bester L, Brown DB, Ryu RK, Sze DY, Rilling WS, Sato KT, Sangro B, Bilbao JI, Jakobs TF, Ezziddin S, Kulkarni S, Kulkarni A, Liu DM, Valenti D, Hilgard P, Antoch G, Muller SP, Alsuhaibani H, Mulcahy MF, Burrell M, Real MI, Spies S, Esmail AA, Raoul JL, Garin E, Johnson MS, Benson AB 3rd, Sharma RA, Wasan H, Lambert B, Memon K, Kennedy AS, Riaz A, Technology Assessment Committee Interventional Oncology Task Force of the Society of Interventional Radiology: Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol* 2011;22:265–278.
- 44 Gulec SA, Pennington K, Hall M, Fong Y: Preoperative Y-90 microsphere selective internal radiation treatment for tumor downsizing and future liver remnant recruitment: a novel approach to improving the safety of major hepatic resections. *World J Surg Oncol* 2009;7:6 Epub 2009/01/10.
- 45 Cao C, Yan TD, Morris DL, Bester L: Radioembolization with yttrium-90 microspheres for pancreatic cancer liver metastases: results from a pilot study. *Tumori* 2010;96:955–958.
- 46 Michl M, Haug AR, Jakobs TF, Paprottka P, Hoffmann RT, Bartenstein P, Boeck S, Haas M, Laubender RP, Heinemann V: Radioembolization with Yttrium-90 microspheres (SIRT) in pancreatic cancer patients with liver metastases: efficacy, safety and prognostic factors. *Oncology* 2014;86:24–32.
- 47 Kagohashi K, Satoh H, Ishikawa H, Ohtsuka M, Sekizawa K: Liver metastasis at the time of initial diagnosis of lung cancer. *Med Oncol* 2003;20:25–28.
- 48 Eldridge L: *Lung Cancer Spread to the Liver*. September 12, 2013; Available from: <http://lungcancer.about.com/od/lungcancermetastases/a/Lung-Cancer-Liver.htm>.
- 49 Murthy R, Mutha P, Lee JH, Oh Y: Yttrium-90-labeled microsphere radioembolotherapy of liver-dominant metastases from thoracic malignancies. *J Vasc Interv Radiol* 2008;19:299–300.
- 50 Gaba RC, Lakhoo J: Yttrium-90 microsphere radioembolization for treatment of lung cancer hepatic metastases. *Case Rep Oncol* 2012;5:479–486.
- 51 Ricke J, Großer O, Amthauer H: Y90-radioembolization of lung metastases via the bronchial artery: a report of 2 cases. *Cardiovasc Intervent Radiol* 2013;36:1664–1669.
- 52 Sharma RA, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, Bower G, Shannon JA, Gibbs P, Steward WP: Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007;25:1099–1106.
- 53 Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, Cardaci G, Gray B: Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol* 2004;88:78–85.
- 54 Weintraub JL, Salem R: Treatment of hepatocellular carcinoma combining sorafenib and transarterial locoregional therapy: state of the science. *J Vasc Interv Radiol* 2013;24:1123–1134.
- 55 ClinicalTrials.gov: *Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer (STOP-HCC)*. 2014 [cited 2014; Available from: <http://clinicaltrials.gov/ct2/show/study/NCT01556490?term=NCT01556490&rank=1..>].
- 56 ClinicalTrials.gov: *Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)*. 2014 [cited 2014; Available from: <http://clinicaltrials.gov/ct2/show/NCT01135056?term=NCT01135056&rank=1..>].