Future Directions in Radioembolization

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15.1 Introduction

Radioembolization with yttrium-90 (^{90}Y) microspheres represents an innovative approach that has gained increasing awareness and clinical use over the past 5–10 years. The minimal toxicity of radioembolization and the ability to discharge the patient on an outpatient basis make the therapy an attractive alternative in the treatment of primary and metastatic liver malignancies. Patients are able to resume normal activities shortly following treatment, with minimal side effects, in contrast to the post-embolization syndrome often associated with current chemoembolic techniques.

Treatment planning requires a multi-disciplinary team with clear leadership and accountability to ensure that the screening, diagnostic and treatment procedures are conducted in a seamless fashion. The essential steps include: (1) calculation of target liver mass to be infused and tumor burden; (2) visceral angiography to map out tumor-perfusing vessels and embolize collaterals; (3) assessment of pulmonary shunt; (4) determination of the optimal therapeutic dose; (5) room preparation; (6) radiation monitoring and safety procedures; (6) calculation of residual activity and efficiency of ^{90}Y delivery.

Careful patient selection and preparation for ^{90}Y liver-directed therapy will result in an optimal risk: benefit ratio for patients. For patients presenting with hepatocellular carcinoma, the treatment of advancing disease must be balanced against the often-compromised functional liver reserve due to underlying cirrhosis. Selection of patients with adequate hepatic reserve and good functional status will maximize the beneficial therapeutic effect of ^{90}Y therapy with minimal risk to normal liver parenchyma. ^{90}Y therapy has also proved to be beneficial for patients presenting with metastatic disease who have intra-hepatic progression despite standard of care chemotherapy.

Depending on the etiology, functional status, hepatic anatomic vasculature and presentation of liver lesions, several factors need to be considered in treatment planning. If re-treatment of the same target area is anticipated, cumulative radiation exposure to the target area should be determined and the radiation dose adjusted accordingly to minimize the risk of radiation-induced hepatitis. If vascularity permits, selective infusion of a segment or lesion will mitigate the risk of radiation exposure to normal tissue. Dose reduction may also be required if estimated pulmonary shunt exceeds 50 Gy over cumulative infusions of ^{90}Y, or if hyperaugmentation of lung shunt is identified. Prophylactic administration of anti-ulcer medication and steroids post-treatment will mitigate the risk of pain from non-target radiation into the gastrointestinal tract and provide the patient with some relief from fatigue, respectively.

Post-procedural follow-up of the patient to assess any treatment-emergent side effects and tumor response is conducted at 30 days and then at 2- to 3-month intervals thereafter. Other than mild to moderate constitutional symptoms, the side effects of radioembolization include non-target radiation, radiation pneumonitis and radiation hepatitis. Diligent vascular mapping during the treatment planning angiogram with embolization of the gastroduodenal and right gastric arteries, as well as other perforating vessels, will minimize the likelihood of inadvertent deposition to gastric structures. As mentioned above, dose reduction and careful consideration of functional liver reserve will mitigate the occurrence of radiation pneumonitis and radiation hepatitis, respectively.

Two devices are commercially available. TheraSphere® (glass microsphere; MDS Nordion, Kanata, Canada) was approved in 1999 by the Food and Drug Administration (FDA) under a Humanitarian Device Exemption (HDE) for the treatment of unresectable hepatocellular carcinoma (HCC) in patients who can have appropriately positioned hepatic arterial catheters with or without portal vein thrombosis [1]. SIR-Spheres® (resin microsphere; Sirtex Medical, Lane Cove, Australia) were granted full pre-marketing approval in 2002 by the FDA for the treatment of colorectal metastases in conjunction with intra-hepatic FUDR [2]. Both devices have European approval for liver neoplasia and approvals in various Asian countries.

The aim of this chapter is to briefly review the background and early work with radioembolization, as well as to discuss future research opportunities.

15.2 Background

Investigations into ^{90}Y and other radioisotopes for the treatment of cancer date back to the 1960s [3, 4]. Initial studies of resin ^{90}Y in humans were reported in the late 1970s. Seminal work in a canine liver model demonstrating the safety and feasibility of using ^{90}Y therapy for hepatic malignancies was reported in the late 1980s [5, 6]. Human studies of ^{90}Y microsphere therapy in liver applications followed from the late 1980s through the 1990s [5–16]. These investigations established the safety of ^{90}Y for intrahepatic applications and the optimal dosimetry for tumor radiation kill, while minimizing exposure to normal liver tissue. The assessment of potential pulmonary shunt, particularly in patients presenting with hepatocellular carcinoma (HCC) was reinforced in these studies. The importance of embolizing collateral vessels such as the gastroduodenal and right gastric arteries to prevent reflux to the gastric structures was also realized. Gastric ulceration requiring surgical intervention was routinely reported in many of these studies.

15.3 Early Clinical Work

As early as 1963, researchers were investigating the utility of ^{90}Y microspheres in canine prostates [4]. In 1967, Flynn assessed the role of ^{90}Y microspheres for the treatment of lung malignancies [3]. Ariel described initial results of ^{90}Y microspheres with indications, as well as experience with intra-arterial injection of microspheres for the treatment of unresectable pancreatic cancer [7–9]. These agents have also been used for splenic injection in a patient with lymphoma, cerebral infusion for brain tumors, extremity infusions for osteogenic sarcomas, and synovial injection for pain [10–17]. Seminal work performed by investigators established the proof of principle of radioactive intra-arterial injection for the treatment of liver tumors using various radioconjugates including ^{90}Y, ^{32}P, Rhenium and Holmium [15, 18–29]. Direct intratumoral injection and portal venous injection of ^{90}Y have been studied, both techniques demonstrating antitumoral activity [30–32]. Magnetic guided microspheres have also

been investigated [33–35]. Anti-tumor effects of ^{90}Y are well-established in patients with lymphoma, as well as in combination with bone tracers [36–38]. Non-radioactive glass microspheres have been studied in rabbit kidneys [39]. Splenic radioembolization with ^{90}Y has also successfully been used for the treatment of hypersplenism and thrombocytopenia [40]. Investigators studied the effects of radiosensitizers combined with ^{90}Y resin microspheres, concluding that BUDR could produce acceptable toxicities in a canine model suggesting that clinical studies of this combination are not excessively toxic [6]. The same group studied ^{90}Y glass microspheres in canines were found to produce portal changes similar to those observed in humans after external beam therapy. Radiation exposures in excess of 300 Gy did not cause total hepatic necrosis and were compatible with survival. The authors concluded that hepatic exposures to humans of 50–100 Gy by ^{90}Y microsphere injection would appear to be feasible and tolerable [5].

15.4 Future Direction

15.4.1 Liver Dominant Breast and Colorectal Metastases

There have been significant advances in the treatment of both primary breast and colorectal carcinoma with the thymidylate synthase inhibitors (e.g. 5 FU, FUDR, capecitabine) that are known to be radio-sensitizers [41]. The typical treatment paradigm involves resection of the primary, followed by chemotherapy (positive lymph nodes) or radiation (positive margins) in the case of breast carcinoma, or radiation of the surgical bed given local recurrence of colorectal malignancy. The most typical sites of distant metastases following breast cancer resection include the liver, bone and brain, and for colorectal cancer primary, the liver and lungs. The natural course of disease appears to be improved and altered by improved chemotherapy agents, with the liver metastases representing the life-threatening condition.

Historical approaches to treatment of liver metastases have included administration of the thymidylate synthase inhibitors in an attempt to delay further disease progression. Stabilization of disease has ranged from 6 to 8 months; however, inevitably, all patients demonstrate progression on these regimens [42]. Preliminary data in the application of ^{90}Y microspheres for liver dominant colorectal and breast metastases are very encouraging by classic RECIST and ^{18}FDG-PET imaging [43–47]. Given the low toxicity profile for ^{90}Y relative to the standard of care chemotherapy regimens, patients tolerate the therapy exceedingly well.

Presently, the tolerability of systemic agents and ^{90}Y is being investigated [48]. There are known radio-sensitizing properties of thymidylate synthetase inhibitors, and potential for radiation induced liver toxicity due to the synergistic effects. This synergism may present some interesting opportunities to further extend the therapeutic benefit of ^{90}Y therapy. There is a precedent for this approach in the treatment of breast, pancreatic, colon, liver and other malignancies. The principle of enhanced tumor response and time to disease progression using a combination of radio-sensitizing agents and external beam ionizing radiation is well established [49]. Clearly, additional assessment of toxicity, maximum tolerated dose (dose escalation), and the optimal therapeutic window will need to be explored under carefully controlled studies before widespread clinical application is considered.

Other studies to be considered include the combination of liver-directed therapy, such as ^{90}Y, with current standards of care, including bevacizumab and cetuximab. Although growth factor inhibitors may indeed play a role in controlling tumor growth, the vascular effects may affect the applicability of transarterial therapies. Growth factor inhibitors (bevacizumab, cetiximab) may inhibit the ability to treat liver tumors by deleteriously affecting the vasculature. Studies combining chemotherapy agents FOLFOX or 5 FU/LV/irinotecan (FOLFIRI) with and without ^{90}Y (first or second line) may show promise in further extending survival, currently over 20 months [41].

15.4.2 Neuroendocrine Liver Metastases

Neuroendocrine tumors typically arise in the endocrine glands and cells that are located throughout the body. The most common types include carcinoid, gastroenteropancreatic, and adrenal. The most common primary sites for carcinoid tumors include the gastro-

intestinal tract or the lungs; they may also arise in the pancreas. Other neuroendocrine tumors may originate from anywhere in the body. Gasteroenteropancreatic (GEP) tumors that most commonly originate in the cells of the stomach, intestines or pancreas, may be further categorized into gastrinomas, glucagonomas, insulinomas, vasoactive intestinal polypeptide tumor (VIPoma) and somatostatinomas. There is also a class of multiple endocrine neoplasia syndromes (MEN 1 and MEN 2), which are usually genetically based, and increase the likelihood of developing GEP tumors. Carcinoid tumors, particularly if they metastasize to the liver, may result in the excessive production of serotonin and produce carcinoid syndrome. This condition is characterized by diarrhea, flushing of the skin and asthma-like breathing difficulties. Loss of appetite and weight loss may also result.

The intent of neuroendocrine treatments is to reduce tumor burden and where necessary, eliminate or reduce the symptoms resulting from excessive production of hormones, and prolong life. Classic treatments for neuroendocrine tumors that have metastasized to the liver include surgery (resection) or transplantation and the administration of somatostatin analogues such as octreotide or lanreotide. Other approaches include ablative techniques (cryoablation and RFA), bland embolization, TACE, and more recently, ^{90}Y microsphere therapy.

Given the tremendous hypervascularity of neuroendocrine hepatic tumors relative to normal parenchyma, ^{90}Y represents an ideal therapy for palliative reduction of both bulk disease and carcinoid syndrome when this condition presents. Although there are limited published data available on the treatment of neuroendocrine tumors with ^{90}Y microspheres, there are encouraging preliminary results based on its use in clinical practice. The therapy exhibited an excellent safety profile, consistent palliative results and significant debulking. The majority of patients exhibited a partial response on imaging follow-up [50, 51]. Thus, based on this early work, ^{90}Y microspheres appear to provide a low toxicity alternative with some clinical benefit as measured by both tumor response and symptom reduction. Randomized controlled studies of ^{90}Y vs. current standard of care (e.g. surgical resection or somatostatin analogues), or in combination with octreotide are warranted. End points might include time-to-progression, tumor response, improvement in tumor markers (chromogranin A), or clinical benefit (improvement in symptoms).

15.4.3 Mixed Neoplasia/Quality of Life

Another area worthy of future investigation is the treatment of non-colorectal, non-neuroendocrine cancers metastatic to the liver. Often referred to as mixed neoplasia, these refer to patients with liver-dominant metastatic disease to the liver from various primaries (breast, melanoma, pancreas, and lung). Although several reports have been described, controlled phase II studies using time-to-progression, tumor response, or progression-free-survival would be clinically relevant given the dearth of options for some of these patients [51–54].

Survival is the gold standard by which the efficacy of any liver-directed therapy would ideally be measured. However, the resource costs and lengthy studies required to achieve this endpoint in a constantly evolving state-of-the art paradigm make this a daunting task. There is clearly a need to develop surrogate measures of efficacy pending the refinement of technology, treatment techniques and operator expertise so that the treatment effect in randomized studies is validated to the satisfaction of scientists, statisticians and clinicians. Tumor response provides a quantitative measure that has been historically touted as a viable alternative; however, the correlative studies linking tumor response to extended survival have not been forthcoming. Quality of life has gained increasing awareness as a potentially useful measure of treatment efficacy. For those patients who undergo systemic chemotherapy and external radiation as part of the treatment regimen, quality of life with respect to time commitment and side effects certainly impact their quality of life. The incorporation of carefully designed and validated quality of life measures in prospective randomized controlled trials of ^{90}Y is another fruitful area of investigation. Time-to-progression and progression-free-survival represent alternate endpoints that may balance the need for clinically relevant data with the option of patients who progress on therapy to try other experimental agents. Finally, although new and evolving treatments might ideally be compared to a no-treatment control arm, the ethical and moral issues in an increasingly aware patient base make the likelihood of accomplishing this quite low.

15.4.4 Extra-hepatic Applications

The potential applications of ^{90}Y therapy to areas outside the liver are numerous. Any site in the body that is angiographically accessible may potentially be considered for ^{90}Y therapy. This would include: meningiomas, glioblastoma multiforme, renal cell carcinomas, head/neck and lung tumors. Given that skin necrosis following ^{90}Y has been described, the cutaneous contribution of the extra-hepatic vasculature being examined would have to be taken into consideration [14]. Clearly, very carefully controlled in-vitro, animal and phase I safety studies with small patient cohorts are required before widespread clinical applications in these areas are explored.

15.4.5 Combination Therapies

Given the encouraging safety and therapeutic benefit of ^{90}Y in both primary and metastatic liver disease, there is an opportunity to explore its application in combination with other available therapies. Studies to assess the potential synergistic therapeutic benefit of ^{90}Y and known radio-sensitizers in both metastatic breast and colorectal cancer are warranted. Combination capecitabine and ^{90}Y present a low toxicity option for breast cancer patients. The potential to improve hepatic tumor response via the synergistic action of selective uptake of 5-FU in the presence of radiation warrants further investigation. ^{90}Y in combination with 5-FU, FUDR and capecitabine in colorectal metastases to the liver require further study. Given the potential for "super irradiation" of liver parenchyma in the presence of these agents, carefully controlled Phase I dose escalation studies are required.

Combinatorial applications of ^{90}Y and ablative techniques such as RFA and cryo-ablation may provide an option for those patients who would otherwise require surgical resection, but are at high surgical risk due to co-morbidities or prefer less invasive means of treating their disease. ^{90}Y has been shown to reduce tumor burden in downstaging to transplant or resection for HCC patients [55–57]. In patients presenting with tumors which are not amenable to ablative therapy due to excessive size (6–8 cm), ^{90}Y microspheres could be used to reduce these lesions (< 3 cm), followed by the use of ablative therapy to effect further response. This presumes that viable tissue is still present after ^{90}Y therapy. There is strong evidence that ^{90}Y treatment typically results in complete necrosis of the lesion(s) treated [56, 58]. A prospective randomized study comparing time-to-progression or progression-free survival of ^{90}Y vs. RFA in lesions 3–5 cm would provide important information concerning this question.

Combinatorial ^{90}Y and TACE presents an interesting opportunity to assess the cumulative effect of these modalities in effecting tumor kill. Intra-arterial infusion of ^{90}Y in an aerobic environment (non-stasis) could be followed by TACE after the radioactive effect diminishes to sub-therapeutic levels (approximately 2 weeks post ^{90}Y treatment). TACE administration with cytotoxic tumor exposure in a hypoxic environment would then address any viable (radioresistant) cells that remained.

Another possible area of investigation includes the prophylactic radioembolization of remnant liver tissue in patients undergoing hepatic resection for HCC or colorectal metastases. Although initially attractive, this approach may hinder and limit the ability for future ^{90}Y to the prophylactically radioembolized lobe. Furthermore, the blood supply to small metastases is derived from the portal vein, not the hepatic artery, bringing into question whether prophylactic treatment would yield any radiation effect to microscopic metastases [59]. Therefore, if such a study is undertaken, since imaging of micrometastases is not possible, improved survival or decreased time to disease recurrence would represent possible endpoints. It is clear that further research is needed to address possible treatment options for advanced stage HCC. Any studies in this patient population require careful consideration of the risk of therapy induced liver failure vs. the benefit of lesion stabilization.

15.4.6 Liver Transplantation/HCC

One of the most fruitful areas for further research is the application of ^{90}Y in the transplant population. One study has shown that HCC patients presenting with stage T3 lesions can be downstaged to T2 (Milan criteria) in over 50% of cases [56]. Larger prospective randomized controlled studies comparing ^{90}Y to other available therapies (e.g. RFA and TACE) are also warranted. The incidence of HCC continues to rise. Given earlier detection of HCC, with the intent of curative liver transplantation, there will be a sig-

nificant need for alternative downstaging options. The ultimate question that remains unanswered is whether survival would be significantly extended for downstaged patients who receive transplant compared to those who initially present with T2 disease. Only large prospective randomized controlled studies with well established therapies will begin to provide the answers to this question. Also, given the recent developments with sorafenib, combination ^{90}Y with this agent will be of utmost interest.

15.4.7 Dosimetry/Imaging Microspheres

Improved dosimetry planning (translating into enhanced efficacy) for ^{90}Y (or other radioactive agent such as Rhenium-188) should be the focus of research in the next few years [60–62]. These could come in the form of enhanced ^{99m}Tc-MAA particles, or in the development of planning resin or glass microspheres. This would allow the direct calculation of tumor as well as normal parenchymal exposure following ^{90}Y treatment. Direct knowledge of this would allow administration of sufficient ^{90}Y radioactivity that would result in tumoricidal doses with minimal exposure to normal parenchyma. This may then evolve into the ability to perform repeated and scheduled ^{90}Y treatments in a manner analogous to TACE, without the associated risks of radiation hepatitis. The ability to image the microspheres (cold or hot) using imaging techniques such as MRI would also prove clinically useful in the dose planning and clinical follow-up stages. Investigation in advanced imaging of microspheres will lead to enhanced dosimetry (at the tumor level), treatment planning and post treatment imaging [63, 64]. Microspheres with different specific activities and a variable embolic load may permit treatment planning on an individual basis.

15.4.8 Radiation Pneumonitis

The basic assumption of ^{90}Y infusion and dosimetry is the homogeneous distribution of microspheres, throughout the hepatic parenchyma resulting in the same radiation dose to the volume targeted for treatment. Some arteriovenous shunting within tumor is inevitable. Since tumors are fed almost exclusively by hepatic vasculature and are hypervascular relative to normal parenchyma, it may be possible to lower the calculated dose to tumor, thereby permitting treatment of patients with elevated lung shunting.

The package insert for glass microspheres dictates that patients receive no greater than 16.5 mCi or 30 Gy cumulative radiation absorbed dose [1]. The resin microsphere package insert provides guidance on dose reduction for elevated lung shunting; patients with lung shunt fractions greater than 20% should not be treated [2]. These recommendations should be viewed as guidelines since the peer-reviewed published lung limitation is 30 Gy per treatment and 50 Gy cumulative lung dose [65]. There are methods of modifying the approach to dosimetry in order to treat most patients with elevated lung shunt in a safe manner. Now that radioembolization is becoming more accepted as a therapeutic modality, lung dosimetry should be refined in order not to exclude patients from therapy based on dosimetry models that may benefit from improvements.

15.4.9 Response Assessment

The imaging evaluation following radioembolization is difficult by CT or MRI [66, 67]. PET scanning has emerged as an integral imaging modality in the assessment of treatment response to ^{90}Y. While CT provides anatomic information on tumor burden, PET is better at characterizing the functional status of the tumor, both prior to and following treatment. In several studies published, metastatic colorectal liver lesions were evaluated using CT and PET before and after successful ^{90}Y treatment. PET was found to be consistently superior at assessing tumor response to therapy compared to CT [68–71]. Moreover, reduction in metabolic activity measured by PET was correlated with a reduction in CEA. Portal vein retraction has also been described as a secondary sign of response of HCC to ^{90}Y therapy [72].

Traditional methods for the evaluation of tumor response to therapy have been size reduction on CT through the application of the WHO or Response Evaluation Criteria in Solid Tumors (RECIST) criteria [73, 74]. However, some pitfalls may occur when those methods based on CT dimensional changes are applied to ^{90}Y therapy. First, RECIST or WHO criteria do not allow for the use of PET scanning in the follow-up evaluation, thereby ignoring the functional nature of the residual tissue. Further-

more, since ^{90}Y treatment is a highly targeted form of radiation therapy, it may at times lead to tumor necrosis, edema and peri-tumoral hemorrhage, resulting in an increase in tumor size. By RECIST or WHO criteria, this might suggest stabilization of tumor or progression, rather than response. However, upon closer analysis and correlation to PET, investigators have found the reverse to be true [68–70]. Furthermore, some have shown that traditional CT techniques can be misleading and underestimate the true metabolic response of ^{90}Y [69, 70, 75, 76]. In fact, the conclusions of the Barcelona – 2000 EASL conference noted that extensive tumor necrosis is not typically paralleled by a reduction in tumor diameter [74]. The recommendations from this expert panel suggested the estimation of tumor response following ablative therapies should include necrosis and lack of enhancement. This is also true for radioembolization.

Therefore, in patients being treated with ^{90}Y, standard evaluation and follow-up should include liver functions, tumor markers, and imaging on CT or MRI with assessment of lack of enhancement and necrosis. However, in patients with secondary malignancies such as colon cancer, the importance of a sound knowledge of CT findings and imaging pitfalls following ^{90}Y, as well as the necessity of including PET cannot be understated [69–71]. The applicability of functional imaging in the follow-up of the ^{90}Y patient is undergoing further investigation, including diffusion weighted MRI [64].

15.4.10 Portal Vein Thrombosis

Patients with portal vein thrombosis (PVT) tend to be neglected from trans-arterial options. The incidence of this finding is not uncommon, especially given that 1/3 of all HCCs exhibit PVT, and that new agents such as bevacizumab may cause PVT in metastases patients. The recently published American Association for the Study of Liver Disease Practice Guideline for the management of HCC has identified a subgroup of patients within the Barcelona Clinic Liver Cancer (BCLC) staging system who present with advanced stage disease characterized by clinical symptoms and vascular invasion, including portal vein thrombosis [77]. The challenge in treating patients with portal vein thrombosis using embolic type therapy is the risk of liver failure due to compromise of both portal and hepatic flow. Preliminary studies have shown that ^{90}Y can be safely administered in patients with portal vein thrombosis, if microsphere infusion is not taken to angiographic stasis of the tumor bed [78]. Moreover, in the case of single portal branch occlusion in the absence of main occlusion, embolic agents may be considered if patients are selected carefully and hepatopedal flow is present. This presents an opportunity to assess the relative safety and efficacy of ^{90}Y vs. a number of agents in a prospective randomized paradigm in patients with PVT.

15.4.11 Hepatico-enteric Anastomoses/Biliary Stents

Another group that tends to be underrepresented in trans-arterial therapies is that of patients who have undergone previous biliary surgery, hepatico-enteric anastomoses, or biliary stents. It is well recognized that these patients are at high risk for infection following embolic and ablative therapies [79–81]. Given that blood supply to the biliary tree is via the 30-μm peribiliary plexus, ^{90}Y microspheres may potentially flow into and have an effect on the biliary tree. When a patient has been stented or has undergone surgery with violation and disruption of the ampulla of Vater, the biliary tree is colonized, creating a nidus for infection. Decompressing the biliary tree with endoscopic stents or percutaneous transhepatic cholangiography should not be assumed to reduce the risks associated with ^{90}Y use. Controlled studies investigating the role of ^{90}Y in these patients should be considered.

15.5 Conclusion

There are continuing challenges and opportunities in the ^{90}Y treatment of liver disease. Several phase I studies using ^{90}Y microspheres in combination with infusional chemotherapy regimens in metastatic colorectal cancer to the liver have demonstrated very effective tumor response and stabilization of disease [48]. However, the use of these regimens must be tempered against the neurologic, hematologic and GI toxicities that result. Whether the synergistic effect of ^{90}Y and radiosensitizers outweighs the risk of increased toxicity remains to be

determined. The final determination of safety and efficacy will await the completion of randomized controlled trials comparing combinatorial ^{90}Y and chemotherapy vs. chemotherapy alone.

The unique aspect of ^{90}Y therapy is its minimal toxicity profile and highly effective tumor kill and minimal exposure to normal liver tissue in properly selected patients. These unique characteristics in conjunction with the minimally invasive nature provide an attractive option for patients for whom there are few alternatives. The technical and clinical demands of patient selection, treatment planning, ^{90}Y administration and clinical follow-up require a dedicated interdisciplinary team willing to work cooperatively to achieve the best result for the patient. The clinical benefit and potential for enhancing quality of life for the patient given this commitment present an exciting research opportunity for the field of interventional oncology.

References

1. TheraSphere (2004) TheraSphere Yttrium-90 microspheres package insert, MDS Nordion, Kanata, Canada
2. SIRTeX Medical (2004) SIR-Spheres Yttrium-90 microspheres package insert, SIRTeX Medical, Lane Cove, Australia
3. Flynn WJ (1967) The treatment of pulmonary metastases with microspheres of yttrium 90. Minerva Med 58:4498–4500
4. Greene WM (1963) Embolization of dog prostates with yttrium-90 microspheres. J Urol 90:451–457
5. Wollner I, Knutsen C, Smith P, Prieskorn D, Chrisp C, Andrews J, Juni J, Warber S, Klevering J, Crudup J, Ensminger W (1988) Effects of hepatic arterial yttrium 90 glass microspheres in dogs. Cancer 61:1336–1344
6. Wollner IS, Knutsen CA, Ullrich KA, Chrisp CE, Juni JE, Andrews JC, Tuscan MJ, Stetson PL, Ensminger WD (1987) Effects of hepatic arterial yttrium-90 microsphere administration alone and combined with regional bromodeoxyuridine infusion in dogs. Cancer Res 47:3285–3290
7. Ariel I (1965) Intra-arterial injection of radioactive microspheres of ceramic in the treatment of malignant tumors. Indications and clinical results. Minerva Med 56:2030–2037
8. Ariel IM (1965) Treatment of inoperable primary pancreatic and liver cancer by the intra-arterial administration of radioactive isotopes (Y90 radiating microspheres). Ann Surg 162:267–278
9. Ariel IM, Flynn W, Pack GT (1967) Current possibilities of radioactive ceramic microspheres labeled with yttrium 90. Minerva Med 58:4496–4498
10. Ariel IM, Padula G (1973) Irradiation of the spleen by the intra-arterial administration of 90 yttrium microspheres in patients with malignant lymphoma. A preliminary report. Cancer 31:90–96
11. Simon N, Siffert R, Baron MG, Mitty HA, Rudavsky A (1968) Preoperative irradiation of osteogenic sarcoma with intra-arterially injected yttrium-90 microspheres. Case report. Cancer 21:453–455
12. Jaffe R, Simon N (1968) Treatment of brain tumors with internally deposited yttrium 90. Neurology 18:309
13. Pandey U, Bapat KN, Samuel G, Sarma HD, Chaudhari PR, Dhami PS, Kannan R, Venkatesh M (2005) Evaluation of 90Y phosphate particles as a possible radiation synoviorthesis agent. Nucl Med Commun 26:459–463
14. Sojan S, Bartholomeusz D (2005) Cutaneous radiation necrosis as a complication of yttrium-90 synovectomy. Hell J Nucl Med 8:58–59
15. Dunn AL, Manco-Johnson M, Busch MT, Balark KL, Abshire TC (2005) Leukemia and P32 radionuclide synovectomy for hemophilic arthropathy. J Thromb Haemost 3:1541–1542
16. Chadzopoulos D, Badiavas K (2005) Complications in ^{90}Y radiation synovectomy. Hell J Nucl Med 8:134; author reply 134
17. Sheppeard H, Aldin A, Ward DJ (1981) Osmic acid versus yttrium-90 in rheumatoid synovitis of the knee. Scand J Rheumatol 10:234–236
18. Chamberlain MN, Gray BN, Heggie JC, Chmiel RL, Bennett RC (1983) Hepatic metastases – a physiological approach to treatment. Br J Surg 70:596–598
19. Mantravadi RV, Spigos DG, Tan WS, Felix EL (1982) Intraarterial yttrium 90 in the treatment of hepatic malignancy. Radiology 142:783–786
20. Mantravadi RV, Spigos DG, Karesh SM, Pavel DG, Grady EG, Capek V (1983) Work in progress: intra-arterial P-32 chromic phosphate for prevention of postoperative liver metastases in high-risk colorectal cancer patients. Radiology 148:555–559
21. Hafeli UO, Casillas S, Dietz DW, Pauer GJ, Rybicki LA, Conzone SD, Day DE (1999) Hepatic tumor radioembolization in a rat model using radioactive rhenium (^{186}Re/^{188}Re) glass microspheres. Int J Radiat Oncol Biol Phys 44:189–199
22. Nijsen F, Rook D, Brandt C, Meijer R, Dullens H, Zonnenberg B, de Klerk J, van Rijk P, Hennink W, van het Schip F (2001) Targeting of liver tumour in rats by selective delivery of holmium-166 loaded microspheres: a biodistribution study. Eur J Nucl Med 28:743–749
23. Vuorela J, Kauppinen T, Sokka T (2005) Distribution of radiation in synovectomy of the knee with ^{166}Ho-FHMA using image fusion. Cancer Biother Radiopharm 20:333–337
24. Yan L, Li L, Chen S (1996) Radioembolization with 32P-labelled glass microspheres for advanced hepatocellular carcinoma. Zhonghua Wai Ke Za Zhi 34:526–529
25. Yan L, Li Z, Li L, Wang L, Lu W, Xie X, Liang Z (2000) The relationship between effects and radiation doses of intra-arterial phosphorus-32 glass microspheres embolization therapy for patients with advanced liver cancer. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 38:837–840
26. Keng GH, Sundram FX, Yu SW, Somanesan S, Premaraj J, Oon CJ, Kwok R, Htoo MM (2002) Preliminary experience in radionuclide therapy of hepatocellular carcinoma using hepatic intra-arterial radio-conjugates. Ann Acad Med Singapore 31:382–386

27. Kumar A, Bal C, Srivastava DN, Thulkar SP, Sharma S, Acharya SK, Duttagupta S (2006) Management of multiple intrahepatic recurrences after radiofrequency ablation of hepatocellular carcinoma with rhenium-188-HDD-lipiodol. Eur J Gastroenterol Hepatol 18:219–223
28. Kumar A, Srivastava DN, Bal C (2006) Management of postsurgical recurrence of hepatocellular carcinoma with rhenium 188-HDD labeled iodized oil. J Vasc Interv Radiol 17:157–161
29. Yoon CJ, Chung JW, Park JH, Kim YI, Lee KH, Jeong JM, Paeng JC (2004) Transcatheter arterial embolization with ^{188}Rhenium-HDD-labeled iodized oil in rabbit VX2 liver tumor. J Vasc Interv Radiol 15:1121–1128
30. Lin WY, Tsai SC, Hsieh JF, Wang SJ (2000) Effects of ^{90}Y-microspheres on liver tumors: comparison of intratumoral injection method and intra-arterial injection method. J Nucl Med 41:1892–1897
31. Yan ZP, Lin G, Zhao HY, Dong YH (1993) Yttrium-90 glass microspheres injected via the portal vein. An experimental study. Acta Radiol 34:395–398
32. Tian JH, Xu BX, Zhang JM, Dong BW, Liang P, Wang XD (1996) Ultrasound-guided internal radiotherapy using yttrium-90-glass microspheres for liver malignancies. J Nucl Med 37:958–963
33. Hafeli UO, Sweeney SM, Beresford BA, Humm JL, Macklis RM (1995) Effective targeting of magnetic radioactive ^{90}Y-microspheres to tumor cells by an externally applied magnetic field. Preliminary in vitro and in vivo results. Nucl Med Biol 22:147–155
34. Hafeli UO, Sweeney SM, Beresford BA, Sim EH, Macklis RM (1994) Magnetically directed poly(lactic acid) ^{90}Y-microspheres: novel agents for targeted intracavitary radiotherapy. J Biomed Mater Res 28:901–908
35. Rudge S, Peterson C, Vessely C, Koda J, Stevens S, Catterall L (2001) Adsorption and desorption of chemotherapeutic drugs from a magnetically targeted carrier (MTC). J Control Release 74:335–340
36. Hernandez MC, Knox SJ (2003) Radiobiology of radioimmunotherapy with 90Y ibritumomab tiuxetan (Zevalin). Semin Oncol 30[6 Suppl 17]:6–10
37. Hernandez MC, Knox SJ (2004) Radiobiology of radioimmunotherapy: targeting CD20 B-cell antigen in non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 59:1274–187
38. Toegel S, Mien LK, Wadsak W, Eidherr H, Viernstein H, Kluger R, Ettlinger D, Kletter K, Dudczak R, Mitterhauser M (2006) In vitro evaluation of no carrier added, carrier added and cross-complexed [^{90}Y]-EDTMP provides evidence for a novel "foreign carrier theory". Nucl Med Biol 33:95–99
39. Araki N, Nagata Y, Fujiwara K, Aoki T, Mitsumori M, Kimura H, Itasaka S, Saitou H, Hiraoka M, Kawashita M, Kokubo T (2001) Evaluation of glass microspheres for intra-arterial radiotherapy in animal kidneys. Int J Radiat Oncol Biol Phys 49:459–463
40. Becker CD, Rosler H, Biasiutti FD, Baer HU (1995) Congestive hypersplenism: treatment by means of radioembolization of the spleen with Y-90. Radiology 195:183–186
41. Mulcahy MF, Benson AB 3rd (2005) Bevacizumab in the treatment of colorectal cancer. Expert Opin Biol Ther 5:997–1005
42. Stathopoulos GP, Rigatos SK, Stathopoulos JG, Xynotroulas JP, Dimou E (2005) Efficacy and tolerability of oxaliplatin plus irinotecan 5-fluouracil and leucovorin regimen in advanced stage colorectal cancer patients pretreated with irinotecan 5-fluouracil and leucovorin. Am J Clin Oncol 28:565–569
43. Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, Cardaci G, Gray B (2004) Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol 88:78–85
44. Van Hazel G, Price D, Bower G, Blanshard KS, Steward WP, Sharma RA (2005) Selective internal radiation therapy (SIRT) plus systemic chemotherapy with FOLFOX4: a phase I dose escalation study. ASCO GI Symposium 2005, Miami, Florida
45. Van Hazel G, Price D, Bower G, Sharma RA, Blanshard K, Steward WP (2005) Selective internal radiation therapy (SIRT) for liver metastases with concomitant systemic oxaliplatin, 5-fluorouracil and folinic acid: a phase I/II dose escalation study. ASCO GI Symposium 2005, Miami, Florida
46. Coldwell D, Nutting C, Kennedy AK (2005) Treatment of hepatic metastases from breast cancer with yttrium-90 SIR-Spheres radioembolization. Society of Interventional Radiology Annual Meeting 2005, New Orleans, LA
47. Rubin D, Nutting C, Jones B (2004) Metastatic breast cancer in a 54-year-old woman: integrative treatment with yttrium-90 radioembolization. Integr Cancer Ther 3:262–267
48. Sharma RA, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, Bower G, Shannon JA, Gibbs P, Steward WP (2007) Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. J Clin Oncol 25:1099–1106
49. Herscher LL, Cook JA, Pacelli R, Pass HI, Russo A, Mitchell JB (1999) Principles of chemoradiation: theoretical and practical considerations. Oncology (Williston Park) 13[10 Suppl 5]:11–22
50. Coldwell D, Nutting C, Kennedy AK (2005) Use of yttrium-90 SirSpheres to treat metastatic unresectable neuroendocrine tumors to the liver. World Congress of Gastrointestinal Cancer 2005, Barcelona, Spain
51. Kennedy A, Coldwell D, Nutting C, Sailer S, Overton C (2005) Hepatic brachytherapy for GI neuroendocrine tumors with Y90 microspheres: long-term USA results. International Congress on Anti-Cancer Treatment 2005, Paris, France
52. Herba MJ, Thirlwell MP (2002) Radioembolization for hepatic metastases. Semin Oncol 29:152–159
53. Herba MJ, Illescas FF, Thirlwell MP, Boos GJ, Rosenthall L, Atri M, Bret PM (1988) Hepatic malignancies: improved treatment with intraarterial Y-90. Radiology 169:311–314
54. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B (1994) Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med 35:1637–1644
55. Kim DY, Kwon DS, Salem R, Ma CK, Abouljoud MS (2006) Successful embolization of hepatocelluar carcinoma with yttrium-90 glass microspheres prior to liver transplantation. J Gastrointest Surg 10:413–416

56. 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 (2006) Yttrium-90 microspheres (TheraSphere(R)) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol 94:572–586
57. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW (2004) Salvage surgery following downstaging of unresectable hepatocellular carcinoma. Ann Surg 240:299–305
58. Kennedy AS, Nutting C, Coldwell D, Gaiser J, Drachenberg C (2004) Pathologic response and microdosimetry of (^{90})Y microspheres in man: review of four explanted whole livers. Int J Radiat Oncol Biol Phys 60:1552–1563
59. Voboril R (2005) Blood supply of metastatic liver tumors: an experimental study. Int Surg 90:71–77
60. Kennedy AS, Dezern W, McNeillie P, England M, Goldner K, Brooks L, Sailer S (2006) Dose selection of resin Y90 microspheres for liver brachytherapy: a single center review. American Brachytherapy Society 2006, Orlando, Florida
61. Rhee TK, Omary RA, Gates V, Mounajjed T, Larson AC, Barakat O, Sato KT, Mulcahy M, Gordon S, Lewandowski RJ, Salem R (2005) The effect of catheter-directed CT angiography on yttrium-90 radioembolization treatment of hepatocellular carcinoma. J Vasc Interv Radiol 16:1085–1091
62. Kumar A, Srivastava DN, Chau TT, Long HD, Bal C, Chandra P, Chien le T, Hoa NV, Thulkar S, Sharma S, Tam le H, Xuan TQ, Canh NX, Pant GS, Bandopadhyaya GP (2007) Inoperable hepatocellular carcinoma: transarterial ^{188}Re HDD-labeled iodized oil for treatment – prospective multicenter clinical trial. Radiology 243:509–519
63. Avila-Rodriguez MA, Selwyn RG, Hampel JA, Thomadsen BR, Dejesus OT, Converse AK, Nickles RJ (2007) Positron-emitting resin microspheres as surrogates of (^{90})Y SIR-Spheres: a radiolabeling and stability study. Nucl Med Biol 34:585–590
64. Deng J, Miller FH, Rhee TK, Sato KT, Mulcahy MF, Kulik LM, Salem R, Omary RA, Larson AC (2006) Diffusion-weighted MR imaging for determination of hepatocellular carcinoma response to yttrium-90 radioembolization. J Vasc Interv Radiol 17:1195–1200
65. Ho S, Lau WY, Leung TW, Chan M, Johnson PJ, Li AK (1997) Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur J Nucl Med 24:293–298
66. Keppke AL, Salem R, Reddy D, Huang J, Jin J, Larson AC, Miller FH (2007) Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. AJR Am J Roentgenol 188:768–775
67. Miller FH, Keppke AL, Reddy D, Huang J, Jin J, Mulcahy MF, Salem R (2007) Response of liver metastases after treatment with yttrium-90 microspheres: role of size, necrosis, and PET. AJR Am J Roentgenol 188:776–783
68. Wong CY, Qing F, Savin M, Campbell J, Gates VL, Sherpa KM, Lewandowski RJ, Nagle C, Salem R (2005) Reduction of metastatic load to liver after intraarterial hepatic yttrium-90 radioembolization as evaluated by [^{18}F]fluorodeoxyglucose positron emission tomographic imaging. J Vasc Interv Radiol 16:1101–1106
69. Wong CY, Salem R, Qing F, Wong KT, Barker D, Gates V, Lewandowski R, Hill EA, Dworkin HJ, Nagle C (2004) Metabolic response after intraarterial ^{90}Y-glass microsphere treatment for colorectal liver metastases: comparison of quantitative and visual analyses by ^{18}F-FDG PET. J Nucl Med 45:1892–1897
70. Wong CY, Salem R, Raman S, Gates VL, Dworkin HJ (2002) Evaluating ^{90}Y-glass microsphere treatment response of unresectable colorectal liver metastases by [^{18}F]FDG PET: a comparison with CT or MRI. Eur J Nucl Med Mol Imaging 29:815–820
71. Lin M, Shon IH, Wilson R, D'Amours SK, Schlaphoff G, Lin P (2007) Treatment response in liver metastases following ^{90}Y SIR-spheres: an evaluation with PET. Hepatogastroenterology 54:910–912
72. Lewandowski RJ, Alli A, Atassi B, Kulik L, Mulcahy MF, Salem R (2006) Retraction of portal vein thrombus following treatment with Y90 TheraSphere: a secondary sign of tumor response. Society of Interventional Radiology 2006, Toronto, Canada
73. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
74. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421–430
75. Bienert M, McCook B, Carr BI, Geller DA, Sheetz M, Amesur N, Avril N (2005) Sequential FDG PET/CT in ^{90}Y microsphere treatment of unresectable colorectal liver metastases. Eur J Nucl Med Mol Imaging 32:723
76. Bienert M, McCook B, Carr BI, Geller DA, Sheetz M, Tutor C, Amesur N, Avril N (2005) ^{90}Y microsphere treatment of unresectable liver metastases: changes in ^{18}F-FDG uptake and tumour size on PET/CT. Eur J Nucl Med Mol Imaging 32:778–787
77. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
78. Salem R, Lewandowski R, Roberts C, Goin J, Thurston K, Abouljoud M, Courtney A (2004) Use of yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. J Vasc Interv Radiol 15:335–345
79. Kim W, Clark TW, Baum RA, Soulen MC (2001) Risk factors for liver abscess formation after hepatic chemoembolization. J Vasc Interv Radiol 12:965–968
80. Thomas KT, Bream PR Jr, Berlin J, Meranze SG, Wright JK, Chari RS (2004) Use of percutaneous drainage to treat hepatic abscess after radiofrequency ablation of metastatic pancreatic adenocarcinoma. Am Surg 70:496–499
81. Geschwind JF, Kaushik S, Ramsey DE, Choti MA, Fishman EK, Kobeiter H (2002) Influence of a new prophylactic antibiotic therapy on the incidence of liver abscesses after chemoembolization treatment of liver tumors. J Vasc Interv Radiol 13:1163–1166