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REVIEW

Selective internal radiation therapy in the management of primary and metastatic disease in the liver

Emma Preston[1]

Nadeem Shaida[2]

Author details can be found at the end of this article

Correspondence to:
Emma Preston;
emma.l.preston@gmail.com

Abstract

Selective internal radiation therapy is a type of brachytherapy used to provide targeted radiotherapy, most commonly to treat primary or metastatic disease within the liver. This review outlines current clinical practice, dosimetric considerations, the pre-treatment workup and safety considerations before treatment. It also examines the clinical evidence for its use in patients with both primary and metastatic disease within the liver.

Key words: Cholangiocarcinoma; Hepatocellular carcinoma; Liver metastases; Radioembolisation; Selective internal radiation therapy; Yttrium-90

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Introduction

Selective internal radiation therapy or transarterial radioembolisation is a type of brachytherapy where radioactive microspheres are injected via catheter into the arterial vasculature surrounding a tumour. The use of selective internal radiation therapy to treat primary and metastatic disease in the liver has grown steadily since the technique was first demonstrated in the 1960s (Ariel, 1965).

Primary hepatobiliary cancer made up 1.9% of all cancer diagnoses in England in 2017 (Office for National Statistics, 2019). The liver is also a frequent destination for metastatic spread from other primary sites, the most common being colorectal (35%), pancreas, oesophagus, duodenum, breast and lung (de Ridder et al, 2016).

Managing tumours within the liver presents two main challenges:

1. Disease often presents at advanced stages not amenable to surgery
2. The sensitivity of normal hepatic tissue often precludes delivering treatment doses of systemic chemotherapy and external beam radiotherapy to malignant tumours.

Transarterial techniques, such as transarterial chemoembolisation and selective internal radiation therapy, exploit the preferential arterial supply of malignant tissue compared to normal hepatic parenchyma. Normal liver tissue takes 70–80% of its blood supply from the portal venous system, whereas 85–100% of the blood supply to primary liver tumours is derived from the hepatic artery, a characteristic shared by metastatic deposits (Breedis and Young, 1954). Selective internal radiation therapy can meet the challenges posed by intrahepatic malignancy by treating or bridging patients to surgery, delivering high radiation (100–3000 Gy) to a precise region of tumour with as little exposure to healthy liver tissue as possible.

Radiopharmaceuticals

The most common radioisotope used in selective internal radiation therapy is yttrium-90 (^{90}Y), although radiopharmaceuticals using other beta emitters such as holmium-166 (^{166}Ho) are also in development (Table 1). In addition to being detectable on single photon emission computed tomography/computed tomography (SPECT/CT), ^{166}Ho is paramagnetic and detectable on magnetic resonance imaging, which has applications in pre-therapy and real-time imaging during administration.

The radioisotope is bound to either glass (TheraSpheres), resin (SIR-Spheres) or plastic (QuiremSpheres) microspheres of a diameter (20–60 µm) that results in the microspheres

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Table 1. Comparison of radioisotopes used in selective internal radiation therapy

Property	Radioisotope	
	Yttrium-90	Holmium-166
Half life	64.1 hours	26.8 hours
Beta particle energy	2.27 MeV (99.9%)	1.77 MeV (48.7%) 1.85 MeV (50.0%)
Gamma ray energy	No gamma emission	81 keV
Maximum tissue penetration depth	10.8 mm	8.7 mm
Mean tissue penetration depth	3.8 mm	2.2 mm
Depth of 90% dose deposition	2.8 mm	2.1 mm
Commercially available microspheres	TheraSpheres SIR-Spheres	QuiremSpheres

From Johnson and Yanch (1991)

becoming preferentially lodged in malignant rather than normal arterioles and prevents them from transiting through the capillary bed to the venous circulation. Resin microspheres have significantly less radioactivity per microsphere than glass microspheres (50 Bq vs 2500 Bq), and so a larger number is required to deliver the same activity as glass (Giammarile et al, 2011).

Pre-treatment clinical assessment

Selective internal radiation therapy is a palliative treatment only considered for patients who have surgically unresectable primary or metastatic disease that is chemotherapy refractory or intolerant to chemotherapy. They should have >3 months of life expectancy, no signs of overt liver failure or active hepatitis, no extensive untreated portal hypertension and an ECOG performance status of ≤2 (ambulatory, capable of self-care but unable to carry out work activities and active >50% of waking hours). Multidisciplinary team discussion is mandatory.

Pre-treatment radiological evaluation

In addition to the functional assessment of liver reserve by the way of liver function tests, patients undergo triphasic liver computed tomography or magnetic resonance imaging to assess the anatomical location and extent of intrahepatic disease, vascular anatomy, tumour volume and liver volume (Figure 1a). Quantifying functional liver reserve for transarterial therapies informs clinicians about the risk of post-radioembolisation syndrome; a triad of fatigue, nausea and abdominal pain that can persist up to 6 weeks after treatment.

Pre-treatment angiography

Before treatment the coeliac and mesenteric vasculature must be mapped, as anatomical variations are common which can compromise the safety and efficacy of selective internal radiation therapy (Figure 1b). Microspheres entering the right gastric, gastroduodenal and cystic arteries can cause post-procedural gastric and duodenal ulcers, pancreatitis and radiation-induced cholecystitis. Some of these arteries may be embolised depending on the planned location of injection and vessel diameter, but this is not routinely practiced. Evidence from case series shows embolisation does not entirely prevent microsphere-induced gastroduodenal ulcers and new hepaticoenteric collaterals can develop post embolisation (Abdelmaksoud et al, 2010).

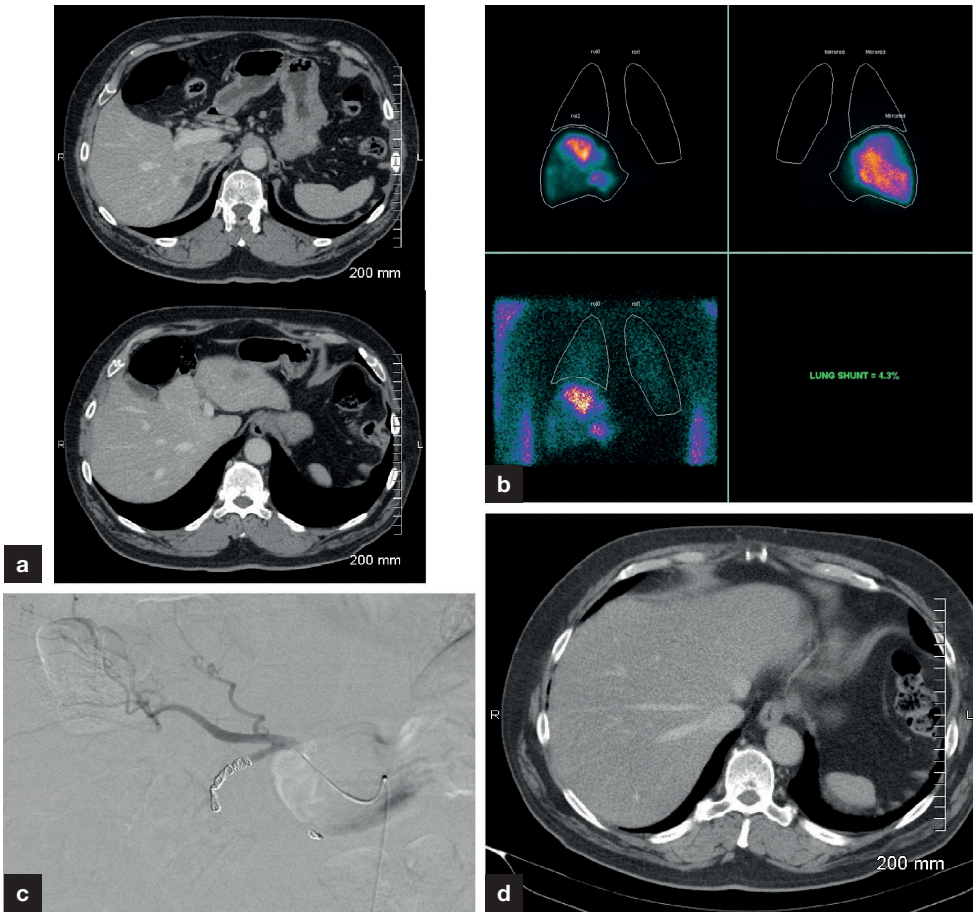

Figure 1. A patient with bilobar liver metastases from colorectal cancer who underwent selective internal radiation therapy. a. Staging computed tomography showing bilobar metastatic disease within the liver. b. Pre-treatment angiography and embolisation of the right gastric and gastroduodenal artery. c. ^{99m}Technetium macroaggregated albumin planar scintigraphy scan results showing activity within the liver and no significant lung shunt. d. Follow-up computed tomography 5 years post-selective internal radiation therapy showing no residual liver disease.

Pre-treatment simulation scanning

Potentially hazardous extrahepatic distribution and lung shunts are identified on planar scintigraphy or SPECT/CT after the injection of ^{99m}Tc-MAA (^{99m}Technetium macroaggregated albumin) (Figure 1c). ^{99m}Tc-MAA emits gamma rays and has similar physical characteristics to ^{90}Y microspheres, mimicking their transit through the liver and hepatopulmonary shunts. Malignant neovascularisation around tumours can increase the degree of lung shunting (Leung et al, 1994).

The degree of hepatopulmonary shunting is quantified by calculating the lung shunt fraction – the proportion of activity counts distributed to the lungs in relation to those from the lung and liver (Leung et al, 1994). Patients with a lung shunt fraction >20% or whose lungs would receive an absorbed dose greater than 30 Gy are at risk of developing radiation-induced pneumonitis and should not be considered for selective internal radiation therapy. Improved modelling of the differential tissue densities in the lung and liver on SPECT/CT more accurately estimates lung absorbed doses than planar scintigraphy; the latter overestimates lung shunt fraction by up to 170% (Yu et al, 2013).

Dosimetry

The dose calculation methods for ^{90}Y microsphere therapies are device specific because of the differing biodistribution between microsphere types. Glass microspheres are assumed to distribute homogenously while resin microspheres distribute heterogeneously within the

liver. For glass microspheres, the desired dose to the liver is between 80 and 150 Gy. There are three different methods to calculate treatment dose for resin microspheres (Table 2), the most widely used and evaluated of which is the body surface area method. The partition method is more patient specific and limits doses based on organs at risk, but is less widely used because of the difficulty in applying it to more complex disease. However, using ^{99m}Tc-MAA SPECT/CT images and the partition method a pre-treatment dose threshold of ≥205 Gy had a sensitivity of 100% and accuracy of 90% in predicting tumour response, and patients had a statistically significant increase in median overall survival (18.2 months ≥205 Gy vs 4.3 months <205 Gy, P=0.005) (Garin et al, 2015). Advanced dosimetry techniques using ^{99m}Tc-MAA SPECT/CT and personalised Monte Carlo dosimetry can better model the heterogeneity of activity distribution in patients and has been shown to recommend maximum prescribed activities based on typical non-tumour and lung dose thresholds at least 27% higher than with the partition method (Petitguillaume et al, 2014). For all calculation methods the lung shunt fraction must be accounted for; those with a significant lung shunt fraction may require a dose adjustment.

^{90}Y procedure and techniques

Dose administration sets are provided by suppliers for safe transportation and use in the clinical setting. Access is gained via percutaneous puncture of the femoral or radial artery, and a catheter is guided to the pre-planned injection site from the ^{99m}Tc-MAA study. Glass microspheres are given via a slow continuous infusion with saline, while resin microspheres are infused intermittently with sterile water or 5% dextrose. This is to avoid stasis during injection, which is more likely a result of the higher number of resin microspheres required to reach the same injected activity as glass. Stasis during injection can lead to incomplete dose delivery and is one of the strongest independent risk factors for the development of gastroduodenal ulceration (P=0.004) (Lam et al, 2013). When compared to sterile water, 5% dextrose reduces the incidence of stasis and results in significantly higher delivery of prescribed activity (Koran et al, 2016).

Follow-up imaging and post-treatment dosimetry

Post-treatment imaging of the upper abdomen is recommended immediately after treatment (<24 hours) to assess the biodistribution of microspheres and calculate the delivered dose, using either SPECT/CT or PET/CT. Post-treatment imaging enables early detection of aberrant microsphere delivery and intervention. Follow-up imaging with triphasic liver computed tomography or magnetic resonance imaging must be done no earlier than 3 months post-procedure to best assess the effectiveness of treatment (Figure 1d).

Safety

Safe non-tumour dose thresholds of 80 Gy are suggested for patients with adequate liver function, and 70 Gy in patients with cirrhosis (Bozkurt et al, 2016). Srinivas et al (2014) found a statistically significant association between the normal liver absorbed dose and incidence of two or more severe complications (mean dose 87.2 Gy, P=0.036). Treatment intensification based on partition model dosimetry achieves high tumour doses of >205 Gy with a non-tumour mean absorbed dose limit of 120 Gy without a statistically significant increase in liver toxicity (12% with no intensification vs 6% with intensification, P>0.05) (Garin et al, 2015).

Complications

Since significant extrahepatic and pulmonary shunting is identified in the pre-treatment workup through ^{99m}Tc-MAA scanning, the incidence of complications is low; 0–6.3% for radiation pneumonitis (Leung et al, 1995) and 3.2% for gastroduodenal ulcers (Lam et al, 2013).

Radioembolisation-induced liver disease presents with deranged liver function tests, jaundice and ascites, typically occurring between 2 weeks and 4 months after treatment. Patients most likely to develop radioembolisation-induced liver disease have had previous radiotherapy or chemotherapy from external or transarterial sources and show liver

Table 2. Various methods used to calculate injected activity required to treat for glass and resin microspheres

Method		Equation	Characteristics: Empirical/ personalised	Adjusted for: Tumour load	Liver size	Tumour avidity	Additional information
Glass	Mono-compartmental	Injected activity (GBq) $= \frac{\text{Desired dose (Gy)} \times \text{mass}_{\text{liver}}\text{ (kg)}}{(50 \times (1\text{-LSF}))}$ and LSF (%) × A (Bq) <0.61 GBq	Semi-empirical	No	Yes	No	
Resin	Empirical	Tumour involvement ≤25% = 2.0 GBq Tumour involvement 25–50% = 2.5 GBq Tumour involvement ≥50% = 3.0 GBq	Empirical	Yes	No	No	Not recommended because of toxicity
	Body surface area	BSA (m^2) = 0.20247 × height $(m)^{0.725}$ × weight $(kg)^{0.425}$ Injected activity (GBq) $= (\text{BSA}-0.2) + \left[\frac{\text{volume}_{\text{tumour}}\text{ (L)}}{\text{volume}_{\text{tumour}}\text{ (L)} + \text{volume}_{\text{liver}}\text{ (L)}}\right]$	Semi-empirical	Yes	Yes	No	Most commonly used method
	Partition	Injected activity (GBq) $= \frac{\text{Desired dose(Gy)}\ (\text{T/N} \times \text{mass}_{\text{tumour}}\text{ (kg)} + \text{mass}_{\text{liver}}\text{ (kg)})}{49.670 \times (1\text{-LSF})}$ $\text{T/N} = \frac{\text{activity}_{\text{tumour}}\text{ (GBq)}/\text{mass}_{\text{tumour}}\text{ (kg)}}{\text{activity}_{\text{liver}}\text{ (GBq)}/\text{mass}_{\text{liver}}\text{ (kg)}}$	Personalised	Yes	Yes	Yes	Difficult to apply in diffuse disease

BSA = body surface area; LSF = lung shunt fraction. From Giammarile et al (2011)

dysfunction or cirrhosis before selective internal radiation therapy (Gil-Alzugaray et al, 2013). Radioembolisation-induced liver disease can be detected and monitored through post-treatment monitoring of liver function tests, typically 1 month post-treatment.

Clinical outcomes

Hepatocellular carcinoma

Patients with intermediate and advanced stage hepatocellular carcinoma are often the main candidates for treatment with transarterial therapies in addition to systemic chemotherapy with sorafenib. These patients have scores of Child–Pugh A-B and Barcelona Clinic Liver Cancer (BCLC) B (multinodular, unresectable disease with preserved liver function, ECOG 0) or BCLC C (portal invasion, extrahepatic spread with preserved liver function, ECOG 1-2).

Early pilot studies comparing selective internal radiation therapy to transarterial chemoembolisation showed either similar median progression-free survival (3.6 months vs 3.7 months respectively) (Kolligs et al, 2015) or increased median time to progression (>26 months vs 6.8 months respectively, P=0.0012) (Salem et al, 2016). There was no significant difference in overall survival between selective internal radiation therapy and transarterial chemoembolisation (18.6 months vs 17.7 months respectively, P=0.99) (Salem et al, 2016). Two phase III randomised controlled trials (SARAH and SIRveNIB) have been published comparing the efficacy and safety of selective internal radiation therapy to sorafenib. No significant differences in median overall survival or progression-free survival were found between selective internal radiation therapy or sorafenib treatment in either trial (Table 3) (Vilgrain et al, 2017; Chow et al, 2018). SORAMIC was a phase III trial that compared sorafenib monotherapy to selective internal radiation therapy plus sorafenib. This showed no significant difference in overall survival between the two treatment types (Table 3), although subgroup analysis suggested selective internal radiation therapy provided a survival benefit in younger patients, non-cirrhotic patients and those with non-alcohol-related cirrhosis (Ricke et al, 2019).

Selective internal radiation therapy can also be used to induce hypertrophy in liver tissue and enable bridging to surgery in hepatocellular carcinoma. In a study of 31 patients post-selective internal radiation therapy, median hypertrophy of the future liver tissue remnant before surgery was 23.3% in patients who had a radiation lobectomy and 9% in patients who had a radiation segmentectomy. All underwent hepatic resection and disease control was achieved in 100% of patients, with median recurrence-free survival of 34.2 months (Gabr et al, 2018).

Table 3. Phase III randomised controlled trials comparing sorafenib monotherapy with selective internal radiation therapy alone or as an adjuvant to sorafenib in hepatocellular carcinoma

			n		Median overall survival (months)		*P* value	Median progression-free survival (months)		*P* value
Trial	**C**	**T**	**C**	**T**	**C**	**T**		**C**	**T**	
SARAH (Vilgrain et al, 2017)	Sorafenib	Selective internal radiation therapy	222	237	9.9	8.0	0.18	3.7	4.1	0.76
SIRveNIB (Chow et al, 2018)	Sorafenib	Selective internal radiation therapy	178	182	10.0	8.8	0.36	5.1	5.8	0.31
SORAMIC (Ricke et al, 2019)	Sorafenib	Selective internal radiation therapy + sorafenib	208	216	11.4	12.1	0.95	n/a	n/a	n/a

C = control; T = treatment

Intrahepatic cholangiocarcinoma

Owing to the rarity of patients with intrahepatic cholangiocarcinoma, selective internal radiation therapy has only been evaluated in small patient studies, making assessments of its efficacy in treating intrahepatic cholangiocarcinoma uncertain. A pooled analysis of 11 studies demonstrated that patients treated with selective internal radiation therapy for unresectable intrahepatic cholangiocarcinoma had a median overall survival of 15.5 months, comparable to that of systemic chemotherapy and transarterial chemoembolisation (Al-Adra et al, 2015). These patients can also be downstaged successfully for surgery with selective internal radiation therapy – the treatment with the best outcomes for intrahepatic cholangiocarcinoma. In one study, all five patients who had surgical resection post-selective internal radiation therapy were alive at the end of the study (median follow up 979 days) (Mouli et al, 2013), although surgery may not be appropriate for patients with multifocal disease, as resection was not associated with a survival benefit when compared to transarterial therapies in multivariate analysis (P=0.24) (Wright et al, 2018).

Metastatic disease from colorectal carcinoma

The role for selective internal radiation therapy in metastatic colorectal cancer has been explored in several randomised controlled trials, mainly evaluating selective internal radiation therapy with radiosensitising chemotherapy regimens.

Matched pair comparison between selective internal radiation therapy and best supportive care showed patients had a significantly longer median overall survival (8.3 months vs 3.5 months respectively, P<0.001) (Seidensticker et al, 2012). A multicentre randomised phase III trial with resin ^{90}Y microspheres comparing selective internal radiation therapy plus fluorouracil vs fluorouracil alone showed significantly increased median time to progression (4.5 months vs 2.1 months respectively, P=0.03), but no significant difference in median overall survival (10 months vs 7.3 months respectively, P=0.80) (Hendlisz et al, 2010).

Chemotherapy regimens based on folic acid, 5-fluorouracil and oxaliplatin (FOLFOX) are used as the first-line treatment for unresectable colorectal metastases, and their sensitising effect with selective internal radiation therapy has been investigated in three randomised controlled trials. A combined analysis of these three trials was published in 2017. Patients were randomly assigned either FOLFOX plus selective internal radiation therapy (n=554) or FOLFOX alone (n=549), and when compared there was no significant difference in median overall survival (22.6 months vs 23.3 months respectively, P=0.61) and no significant difference in progression-free survival (11.0 months vs 10.3 months respectively, P=0.11) between the two groups (Wasan et al, 2017). In the SIRFLOX trial, patients who underwent FOLFOX plus selective internal radiation therapy vs FOLFOX alone showed a statistically significant increase in median liver progression-free survival (20.5 months vs 12.6 months respectively, P=0.002) (Van Hazel et al, 2016). Subgroup analysis of the pooled results of all three trials also showed no progression-free survival benefit in patients with liver only metastatic colorectal cancer in the FOLFOX plus selective internal radiation therapy vs FOLFOX alone (11.9 months vs 11.1 months respectively, P=0.066), although it did suggest a survival benefit for patients with right-sided primary disease (Wasan et al, 2017). As a result of this analysis, selective internal radiation therapy with FOLFOX is not recommended as a first-line treatment for metastatic colorectal cancer within the liver.

The impact of radiosensitising chemotherapy with selective internal radiation therapy on bridging metastatic colorectal cancer to surgery has also been studied. For participants in the FOXFIRE trial, FOLFOX plus selective internal radiation therapy did not significantly improve the rates of surgical resection compared to FOLFOX alone (21% vs 18% respectively, P=0.508), despite the histopathology of patients who received FOLFOX plus selective internal radiation therapy demonstrating significantly lower percentages of viable tumour (P=0.034) (Winter et al, 2019).

In the UK a multicentre single-arm registry study of ^{90}Y selective internal radiation therapy was carried out to support commissioning decisions. Subgroup analysis showed that an absence of extrahepatic disease, lower tumour number and lower tumour to liver volume percentage were associated with increased survival benefit (White et al, 2017). Guidance effective from April 2019 marked the start of routine commissioning of selective

Table 4. NHS England criteria for commissioning selective internal radiation therapy in adults with chemotherapy refractory or intolerant metastatic colorectal cancer. Selective internal radiation therapy is generally considered after first-line treatment with chemotherapy fails or is not tolerated

Disease stage and treatment decisions		Patient discussion at a hepatobiliary multidisciplinary team meeting + Histological confirmation of carcinoma with liver specific metastases not amenable to curative liver resection + Unequivocal and measurable computed tomography evidence of liver metastases not treatable with surgery or local ablation with curative intent + Evidence of clinical progression during or following oxaliplatin-based and irinotecan-based chemotherapy, unless intolerant or specific contraindication
Criteria for clinical evaluation	Patient functional status	Life expectancy >3 months + World Health Organization status 0–1
	Previous treatment	No previous radiotherapy to the upper abdomen or right lower thorax + No previous portal venous embolisation or chemo-embolisation
	Clinical conditions	No ascites + No cirrhosis + No portal hypertension
	Biochemical parameters	Serum bilirubin ≤1.5 x upper limit of normal + Neutrophil count >1.5x10^9/litre + Platelets >100x10^9/litre + Albumin ≥30 g/litre
	Tumour	≤ 5 tumours + Percentage tumour to liver volume ≤25% + No extrahepatic metastases

From NHS England Specialised Services Clinical Reference Group for Radiotherapy (2018)

internal radiation therapy for adults with metastatic colorectal cancer limited to the liver, with published criteria for those eligible (Table 4) (NHS England Specialised Services Clinical Reference Group for Radiotherapy, 2018).

Metastatic disease from neuroendocrine tumours

Up to 40–50% of patients with neuroendocrine tumours present with metastases at diagnosis, with those within the liver frequently not amenable to surgery. A systematic review (*n*=870) of patients with unresectable neuroendocrine tumour liver metastases found that when compared to transarterial embolisation or transarterial chemoembolisation, patients treated with selective internal radiation therapy showed higher disease control (50% vs 86% respectively) but shorter median overall survival (36 months vs 28 months respectively), although 19.8% of patients had received transarterial embolisation or transarterial chemoembolisation before selective internal radiation therapy (Jia and Wang, 2018). In a retrospective study of 40 patients with unresectable neuroendocrine tumour liver metastases who underwent selective internal radiation therapy, disease control was achieved in 94% of patients after 3 months, and median overall survival was 24.7 months (Barbier et al, 2016). A phase Ib trial in 13 patients with liver metastases from neuroendocrine tumours receiving selective internal radiation therapy after everolimus and pasireotide showed a median overall survival of 46.3 months and median progression-free survival of 18.6 months (Kim et al, 2018).

Key points

- Selective internal radiation therapy is an interventional technique where radioactive microspheres are injected directly into tumours to deliver highly localised radiotherapy, most commonly within the liver.
- Selective internal radiation therapy is primarily offered to patients with surgically unresectable, chemotherapy refractory or chemotherapy intolerant primary or metastatic liver tumours.
- Yttrium-90 microspheres are the most commonly used radiopharmaceutical and have an acceptable safety profile, providing pre-treatment angiography and ^{99m}Technetium macroaggregated albumin imaging identifies any potentially hazardous extrahepatic distribution to the digestive tract or lungs.
- Selective internal radiation therapy has been evaluated in a wide range of primary tumour types, most notably several randomised controlled trials comparing selective internal radiation therapy to chemotherapy in the treatment of hepatocellular carcinoma and metastatic colorectal carcinoma.

Metastases from other primary sites

The use of selective internal radiation therapy has been explored in metastatic disease from other primaries. Patients with liver metastases from breast cancer may benefit from selective internal radiation therapy treatment, with a pooled analysis of 12 studies (n=452) showing a disease control rate of 81% and mean overall survival of 11.3 months (Feretis and Solodkyy, 2020). Gastrointestinal stromal tumours have historically been thought to be radiotherapy resistant, although patients with soft tissue gastrointestinal stromal tumour metastases may benefit (Joensuu et al, 2015). A small study of 11 patients with metastatic gastrointestinal stromal tumours being treated with tyrosine kinase inhibitors who underwent selective internal radiation therapy showed a median overall survival of 29.8 months and median progression-free survival of 15.9 months (Rathmann et al, 2015).

Clinical evidence for alternative radiopharmaceuticals

The HEPAR phase I dose escalation study using ^{166}Ho microspheres explored the possibility of increased mean whole liver doses (60 Gy) compared to resin microspheres. The phase II trial showed stable disease, complete or partial response in 73% of patients at 3 months, with median overall survival of 14.5 months (Prince et al, 2018).

Conclusions

Selective internal radiation therapy has proven to be a versatile adjunct in the treatment or downstaging of a wide range of unresectable chemo-refractory tumours in the liver. It is safe, with an established preoperative assessment programme to minimise harmful side effects. Future research should be directed towards clarifying uncertainty in patient selection criteria, developing more accurate dosimetric techniques and newer radiopharmaceuticals.

Author details

[1]Department of Vascular Surgery, Lister Hospital, Stevenage, UK

[2]Department of Interventional Radiology, Addenbrooke's Hospital, Cambridge, UK

Conflicts of interest

The authors declare no conflicts of interest.

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