SIRT and the treatment of primary and secondary liver cancer

Liver metastases are the leading cause of death from colorectal cancer (CRC) with a median survival of 19 months when treated with chemotherapy. The increasing incidence of hepatocellular carcinoma and the poor outcomes for intrahepatic cholangiocarcinoma (ICC) also add to the clinical need to develop effective liver-directed treatment strategies.

Surgical approaches have led to prolonged disease control with five-year overall survival rates of over 50%, although only 15-20% of patients presenting with liver metastases are considered resectable. Non-surgical therapies offer the potential for improved disease control. These techniques include microwave and radiofrequency ablation, selective internal radiation therapy (SIRT), trans-arterial chemoembolisation (TACE), bland transarterial embolisation and stereotactic ablative body radiotherapy (SBRT). Recent guidance from NICE compares SIRT and TACE for HCC stating that, in non-randomised series, SIRT has higher response rates and survival outcomes (NICE, MIB 62, 63 2016). In the NHS England Commissioning through Evaluation programme, SIRT is offered to patients with inoperable ICC and patients with advanced CRC who have failed two lines of chemotherapy or are intolerant to chemotherapy.

The recently published SIRFLOX clinical trial compared chemotherapy alone with chemotherapy combined with SIRT in the first-line treatment of metastatic CRC. This study reported an improvement in hepatic progression free survival (PFS) of 7.9 months in patients receiving SIRT, although it failed to reach the primary endpoint of PFS. The safety profile for the combination of SIRT with chemotherapy was as expected and as previously reported, including the safety of hepatic resection following SIRT. The evidence from this study will be further augmented by the pooled analysis of SIRFLOX, FOXFIRE and FOXFIRE Global; overall survival will be reported in 2017 and this will represent outcome data from over 1,000 patients.

Delivery of SIRT and medical devices available

SIRT is a form of arterially delivered brachytherapy, utilising the preferential arterial blood flow to hepatic tumours. The radioisotope $^90$Y emits $\beta$-radiation to a mean tissue penetration of 2.5mm with a physical half-life of 64 hours. The microspheres selectively deliver doses of up to 3000 Gy to malignant lesions within the liver. SIRT is targeted to malignant areas while sparing the normal liver parenchyma, reducing the risk of radioembolisation-induced liver disease (REILD) — the main dose limiting toxicity.

SIR-spheres and Theraspheres are the two currently available devices; QuiremSpheres using holmium-166 (160Ho) microspheres are under investigation in clinical trials. These devices are compared in Table 1. The holmium microspheres can also be directly imaged on MRI as they are paramagnetic.

The procedure for the delivery of SIRT involves two procedures performed on separate days. The work-up procedure requires hepatic angiography and coil embolisation of vascular that goes from the liver to other at risk organs. This ensures targeted delivery of the microspheres to the cancer and sparing of the normal parenchyma (figure 1). The interventional radiologist injects technetium-99m labelled macroaggregated albumin (99mTc-MAA) as a tracer which is imaged by single photon emission CT (SPECT) scan. The images derived from the $^{99m}$Tc-MAA whole body scan can allow calculation of the lung shunt (figure 2) and the $^{99m}$Tc-MAA SPECT/CT confirms the distribution of the surrogate dose and identifies any extrahepatic uptake (figure 3b). In the case of holmium, since this radioisotope has low energy gamma emission, a low dose of the microspheres can be used instead of MAA for the work up procedure.

The imaging performed after the delivery of the microspheres are either $^9$B Bremsstrahlung SPECT/CT (figure 3c) or $^9$Y PETCT (figure 3d). Once optimised, $^9$Y PETCT is considered superior in terms of image quality and resolution.

Patient selection

By the criteria of the Commissioning through Evaluation programme used by NHS England, patients with liver-only or liver-dominant mCRC are considered suitable for SIRT after failing two lines of combination chemotherapy or if they are intolerant of chemotherapy. There is no generally accepted definition of how much extrahepatic disease is permitted. For example, in the SIRFLOX study, first-line patients with WHO performance status of 0-1, life expectancy of greater than three months and limited extrahepatic disease were eligible for SIRT. Liver dominant disease was defined as fewer than five lung nodules of ≤1cm diameter or one lesion ≤1.7cm and limited lymph node involvement. In situ primaries were permitted, but should not be progressive.

General criteria for patients suitable for SIRT are shown in Table 2.

Safety and toxicity

The main reported side effect of SIRT is fatigue, which is usually mild but can persist for several weeks. Acute effects...
of SIRT include abdominal pain, mild fever, nausea and diarrhoea. Patients are required to take a proton pump inhibitor to minimise potential symptoms of gastritis. The risk of microspheres travelling to the lungs, causing cough or breathlessness, is minimised by the MAA scan prior to treatment and careful measurement of the lung shunt. Radiation cholecystitis can occur, although this is very rare and normally resolves without treatment.13 REILD is the main concern that has led to the strict eligibility criteria relating to liver function and clinical characteristics. REILD is defined as jaundice and ascites appearing one to two months after treatment, in the absence of tumour progression or bile duct occlusion. It is more likely to occur with pre-existing cirrhosis or previous exposure to chemotherapy.15 Monitoring is by regular liver function tests and treatment with high-dose steroids may be required to prevent complications. The imaging as described above, along with meticulous angiographic technique, is essential to reduce the risk of extratherapeutic complications.

In the treatment of mCRC, SIRT has been safely combined with radiosensitising chemotherapy. Clinical trials established the safety of combining SIRT with irinotecan,16 capcitabine17 and 5-fluourouracil (5FU) and leucovorin (LV).18 The combination of SIRT with infusional 5FU/LV was subsequently assessed in a randomised phase III trial in patients with liver-only metastases who had progressed on standard systemic therapies. This showed that time to progression was extended by 2.5 months.19 In a phase II-I trial of oxaliplatin-5FU/LV with SIRT in patients with liver metastases from CRC, grade 3/4 neutropenia was the dose limiting toxicity. Two large phase III randomised trials were undertaken using this regimen in the first-line setting. SIRFLOX confirmed the higher rate of haematological toxicity seen in the earlier phase trial, and the profile of expected SIRT-associated adverse events. The EPOCH clinical trial, which randomised patients with mCRC to receive either SIRT or chemotherapy, failed to show a survival benefit for the addition of SIRT.20 SIRT is currently recruiting using glass microspheres (NCT 1483027).21

In HCC, a phase II study combining SIRT with sorafenib as first-line treatment in patients with non-resectable disease showed the regimen was tolerable with good efficacy.22 A retrospective analysis of patients with ICC who had SIRT with concomitant chemotherapy drew similar conclusions23 and further research in these settings is ongoing.

A meta-analysis of 18 trials of SIRT suggested that response rates were higher earlier on in the treatment pathway, although benefit was still seen in the salvage setting.24 Consideration should be given to a variety of factors when combining radiosensitisising chemotherapy with SIRT. These include the extent of intra- and extra-hepatic disease, line of therapy, previous toxicity with systemic therapy and hepatic reserve.

An effective SIRT programme requires a coordinated team including nuclear medicine and medical physics, with careful consideration of radiation protection. Key patient restrictions include avoiding close contact with others for one week, especially with young children and pregnant women. Long journeys (greater than one hour) on public transport should be avoided, including flying for one week; special radiation protection advice should be sought if any emergency surgery is required within 28 days of SIRT.

Future directions

Factors that may improve outcomes from SIRT in the future include:

1. Dosimetry - voxel-based modelling to improve dosimetry is in development.
2. Radiosensitisers - the role of novel radiosensitisers is an ongoing research interest.
3. Hypertrophy of the untreated lobe in potentially operable patients - SIRT offers an alternative to portal vein embolisation in patients with potentially operable hepatic malignancies. The patient also receives treatment for the hepatic metastases in case they do not proceed to resection.

In 2017, the NHS Commissioning through Evaluation will report leading to a commissioning decision by NHS England regarding SIRT. In the same year, overall survival from the pooled data from SIRFLOX, FOXFIRE and FOXFIRE Global will report the outcomes from over 1,000 patients in the first-line metastatic CRC setting.

References

Figure 1
Hepatic angiography and coil embolisation of a patient receiving SIRT. The black arrow indicates the coils inserted to embolise the right gastric artery, the blue arrow indicates coils within the gastroduodenal artery.

Figure 2
$^{99m}$Tc-MAA whole body scan with minimal activity within the lungs and a calculated lung shunt of 3.6%. The tracer $^{99m}$Tc-MAA is injected during the work-up and on whole body imaging activity can be detected within the lungs.
Figure 3a
The axial CT confirms the position of the lesion being treated in a 76-year-old male with metastatic colorectal cancer and a previous hepatic resection.

Figure 3b
$^{99m}$Tc-MAA SPECT/CT confirms distribution of the activity to the liver lesion visible on CT.

Figures 3c and 3d
$^{90}$Y Bremsstrahlung SPECT/CT (figure 3c) and $^{90}$Y PETCT (figure 3d) confirm the dose delivery of microspheres in the left lobe of the liver with sparing of the normal liver.

<table>
<thead>
<tr>
<th>Microsphere device</th>
<th>Sir-spheres</th>
<th>Theraspheres</th>
<th>QuiremSpheres</th>
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<tbody>
<tr>
<td>Activity per sphere (Bq)</td>
<td>50</td>
<td>2500</td>
<td>450</td>
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<tr>
<td>Density g/ml</td>
<td>1.6</td>
<td>3.3</td>
<td>1.4</td>
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<tr>
<td>Matrix material</td>
<td>resin</td>
<td>glass</td>
<td>poly(L-lactic acid)</td>
</tr>
<tr>
<td>Isotope</td>
<td>yttrium-90</td>
<td>yttrium-90</td>
<td>holmium-166</td>
</tr>
<tr>
<td>Radiation emitted</td>
<td>$\beta$</td>
<td>$\beta$</td>
<td>$\beta$ &amp; low energy gamma</td>
</tr>
<tr>
<td>Physical half-life (hr)</td>
<td>64.1</td>
<td>64.1</td>
<td>26.8</td>
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**TABLE 1**
Comparison of the characteristics of microsphere medical devices used to deliver SIRT.

**TABLE 2**
General selection criteria for patients being considered for SIRT.

<table>
<thead>
<tr>
<th>Prior chemotherapy</th>
<th>Evidence of clinical progression during or following standard chemotherapy. Intolerance of chemotherapy</th>
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<tbody>
<tr>
<td>Life expectancy</td>
<td>Life expectancy &gt;3 months</td>
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<tr>
<td>Performance status</td>
<td>0-2</td>
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| Liver function tests | Serum bil ≤1.5 x ULN  
 Albumin ≥30g/dl                                               |
| Extrahepatic disease | Limited extrahepatic disease  
 Primary tumour controlled                                        |
| Liver multi-
disciplinary team | Discussed at MDT and not considered suitable for resection or ablation |
| Other exclusion criteria | Not pregnant/adequate contraception  
 No cirrhosis  
 No portal hypertension  
 No clinical ascites |

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