NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of selective internal radiation therapies (SIRT) within their approved indications for treating hepatocellular carcinoma.

Background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer in England, accounting for 55% of primary liver cancer diagnoses in men and 28% of diagnoses in women[1]. It is commonly associated with cirrhosis (scarring of the liver), which can be caused by viral infections such as hepatitis B or C, excessive alcohol intake, or other diseases that result in chronic inflammation of the liver[2]. The risk of developing HCC is higher in men than in women and increases with age, with the average age of diagnosis of HCC at 66 years[2]. There were 4,925 people (3,235 men and 1,690 women) diagnosed with HCC in England in 2016[3].

Treatment for HCC is dependent on liver function, the distribution and volume of tumours within the liver, portal vein involvement and extra-hepatic metastases. Several staging systems are used including the Barcelona Clinic Liver Cancer (BCLC) system, which incorporates the Child–Pugh assessment of liver impairment, tumour characteristics and performance status (Eastern Cooperative Oncology Group [ECOG] score). The stage at which HCC is detected has a significant impact on survival; people with advanced HCC have a poorer prognosis than people with early stage HCC.

Treatment for HCC depends on the location and stage of the cancer, and how well the liver's function is preserved. Early (BCLC stage A) HCC may be treated with surgery (hepatic resection or liver transplantation), or minimally invasive techniques such as percutaneous thermal ablation (for example radiofrequency ablation) to cure the disease. However, treatment is not curative for many people.

Treatment options for unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC include interventional procedures such as transarterial embolisation (TAE), transarterial chemoembolisation using lipiodol (TACE), transarterial chemoembolisation using drug-eluting beads with doxorubicin or cisplatin (DEB-TACE). Some of the interventional procedures (such as DEB-TACE) may be used as a

treatment for downstaging unresectable intermediate HCC to potentially curative therapy, such as liver resection or transplantation or as a bridge to transplantation.

People for whom the above treatments are not suitable, can have targeted chemotherapy. NICE's technology appraisal guidance on sorafenib for the treatment of advanced hepatocellular carcinoma (TA 474) recommends sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment. NICE's technology appraisal guidance on lenvatinib for untreated, advanced HCC (TA 551) recommends lenvatinib as an option for untreated, advanced, unresectable HCC only for people with Child-Pugh grade A liver impairment and have an ECOG performance status of 0 or 1. NICE's technology appraisal guidance on regorafenib for treating advanced unresectable HCC (TA 555) recommends regorafenib as an option for treating advanced unresectable hepatocellular carcinoma only for people who have had sorafenib, and have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1. Best supportive care is offered if targeted chemotherapy or TACE is not available or appropriate.

The technologies

Selective internal radiation therapies (SIRT) deliver radiation to tumours within the liver via microspheres that are injected into the hepatic artery via a catheter from the femoral artery.

NICE interventional procedures guidance 460 states that current evidence on the efficacy and safety of SIRT for primary HCC is adequate for use with normal arrangements. However uncertainties remain and the guidance also recommends that clinicians should enter all patient details onto the UK SIRT register (launched in 2013)[a].

The SIRT technologies to be appraised are TheraSphere, SIR-Spheres and QuiremSpheres.

- TheraSphere (manufactured by BTG) is a CE marked class III active medical device which is indicated for the treatment of hepatic neoplasia. It comprises glass microspheres containing yttrium-90.

- SIR-Spheres Y-90 resin microspheres (manufactured by Sirtex) is a CE marked class III active medical device which is indicated for the treatment of inoperable liver tumours. It comprises resin microspheres containing yttrium-90.

[a] NHS England's Interim Clinical Commissioning Policy Statement (2013) for selective internal radiation therapy (SIRT) states that SIRT is not routinely commissioned in the treatment of HCC.

- QuiremSpheres (manufactured by Quirem Medical, distributed by Terumo Europe) is a CE marked class III active medical device which is indicated for the treatment of unresectable liver tumours. It comprises polyester microspheres containing holmium-166.

Intervention(s)	Selective internal radiation therapies (SIRT): • TheraSphere • SIR-Spheres • QuiremSpheres
Population(s)	• People with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).
Comparators	Unresectable HCC: • The interventions will be compared with each other • Transarterial embolisation (TAE) • Conventional transarterial chemoembolisation using lipiodol (TACE). • Transarterial chemoembolisation using drug-eluting beads (DEB-TACE) (doxorubicin and cisplatin do not currently have a marketing authorisation in the UK for HCC). For people for whom any transarterial embolisation are inappropriate • Established clinical management without SIRT (including but not limited to target chemotherapy).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • time-to-progression • response rates • rates of liver transplant or surgical resection • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The economic modelling should include the costs associated with any work-up phase to identify patients that are not likely to benefit from SIRT. A sensitivity analysis should be provided without the cost of the work-up phase. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the CE marking. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the CE marking. If the evidence allows the following subgroups will be considered: • People with unresectable HCC for whom treatments for downstaging to resection or transplantation or as a bridge to transplantation are considered appropriate treatment options. • People with unresectable HCC with portal vein thrombosis/involvement.

Related NICE recommendations and NICE Pathways	**Related Technology Appraisals**: Sorafenib for treating advanced hepatocellular carcinoma (2017). NICE technology appraisal guidance 474. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (2018). NICE technology appraisal guidance 551. Regorafenib for previously treated unresectable hepatocellular carcinoma (2019). NICE technology appraisals guidance 555. **Related Interventional Procedures**: Radiofrequency ablation (2003) NICE interventional procedures guidance 2. Selective internal radiation therapy in primary hepatocellular carcinoma (2013) NICE interventional procedures guidance 460. **Related NICE Pathways:** Liver cancers (2016) NICE pathway **Other NICE advice:** TheraSphere for treating operable and inoperable hepatocellular carcinoma (2016) NICE advice MB062. SIR-Spheres for treating inoperable hepatocellular carcinoma (2016) NICE advice MB063.
Related National Policy	Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT) June 2013 B01/PS/a National Service Framework Cancer Department of Health (2016) NHS outcomes framework 2016 to 2017

References

1. National Cancer Registration and Analysis Service (2010) Trends in incidences in primary liver cancer subtypes. Accessed May 2017.
2. Patient (2015) Hepatocellular carcinoma. Accessed May 2017.
3. Office for National Statistics (2016) Cancer registration statistics. Accessed March 2018.
4. Verslype, C., Rosmorduc, O. and Rougier, P., 2012. Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *23* (suppl_7), pp.vii41-vii48.