NHS England

Clinical Commissioning Policy Proposition:

Selective internal radiation therapy (SIRT) for the treatment of chemotherapy refractory or intolerant, unresectable primary intrahepatic cholangiocarcinoma (all ages)

Reference: NHS England

Prepared by NHS England Specialised Services Clinical Reference Group for Radiotherapy CRG

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma is a rare type of primary liver cancer that develops in the bile ducts. It is the second most common type of primary liver cancer after hepatocellular carcinoma (HCC), with around 1,900 new cases diagnosed every year. The incidence of this form of cancer increases with age, with the majority of people diagnosed aged between 70 and 80 years.

About current treatments

Intrahepatic cholangiocarcinoma can be treated with surgery where there is potential for cure and is considered to be the treatment of choice. However, the majority of cases are diagnosed at a stage where the cancer is too advanced for surgery to be effective, this is called unresectable disease. Where this is the case, palliative (non-curative) treatment is offered to manage symptoms and prolong life, including chemotherapy, some surgical procedures (such as bile duct bypass, stent insertion), and best supportive care.

While chemotherapy has been demonstrated to be an effective palliative treatment, sometimes the chemotherapy medicines either don't work or stop working, this is

because the cancer develops resistance to the medicine which is called refractory disease. For some people the side effects of chemotherapy treatments will be so significant that the treatment cannot be tolerated. In both cases, chemotherapy treatment is stopped. At this stage, further treatment options are usually limited to best supportive care.

About the new treatment

Selective internal radiation therapy is a way of giving radiotherapy treatment to cancers in the liver. It involves injecting tiny spheres that contain a radioactive substance into blood vessels in the liver via a tube (catheter). The spheres become lodged in the small blood vessels around the cancer and deliver radiation directly to the cancer cells which destroys them.

What we have decided

NHS England has carefully reviewed the evidence to treat chemotherapy refractory or chemotherapy intolerant, unresectable primary intrahepatic cholangiocarcinoma with selective internal radiation therapy and has concluded that there insufficient evidence to make the treatment available at this time.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission selective internal radiation therapy (SIRT) in the treatment of chemotherapy refractory or chemotherapy intolerant, unresectable primary intrahepatic cholangiocarcinoma (ICC) (all ages).

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether SIRT for the treatment of chemotherapy refractory or chemotherapy intolerant, unresectable primary ICC will not be commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Clinical Indication

ICC is a rare type of primary liver cancer originating in the bile ducts and most patients are diagnosed with unresectable disease. The common signs and symptoms include: jaundice, itching, pale coloured stools, fatigue, abdominal pain and weight loss but these often do not appear until late in the course of the disease making early diagnosis difficult.

It can be treated with surgery where there is potential for cure. However, the majority of cases are diagnosed at a stage where the cancer is too advanced for surgery to be effective, this is called unresectable disease. Where this is the case, palliative (non-curative) treatment is offered to manage symptoms and prolong life, including chemotherapy, some surgical procedures (such as bile duct bypass, stent insertion), and best supportive care.

Currently, chemotherapy treatment using cisplatin and gemcitabine is an effective

first line systemic treatment for patients with advanced and inoperable disease. The 5 year survival rate for unresectable ICC that has spread to other parts of the body is approximately 2%.

Sometimes chemotherapy treatment must be stopped earlier than planned, either because the cancer is refractory to the medicine, or because the side-effects are so significant that treatment becomes intolerable. Where this is the case, further treatment options are very limited and usually aim to manage symptoms and any side effects of treatment, as well as providing pain relief. This type of care is called best supportive care or palliative care.

Intervention

SIRT, which may also be called radioembolisation (RE), is a way of giving radiotherapy treatment to cancer in the liver. It involves injecting glass or resin microspheres that contain a radioactive substance, Yttrium^{90} into the hepatic arteries via a catheter. The microspheres become lodged in the small blood vessels around the tumour and deliver radiation directly to the cancer cells, destroying them.

Yttrium-90 is a beta emitting isotope with a half-life of 64.2 hours and following administration, 94% of the radiation is delivered in 11 days (Murthy et al. 2008). Currently, there are two yttrium-90 microsphere products available to treat unresectable ICC who are chemotherapy-resistant or chemotherapy-intolerant in the UK:

- SIR-Spheres®, which are made of resin; and
- TheraSphere ®, which are made of glass.

In 2015, NICE produced interventional procedures guidance (NICE 2005; NICE 2013b; NICE 2013c). The standard options for palliative treatment include chemotherapy, surgical bypass of the bile duct or the insertion of a stent using surgical, endoscopic or percutaneous techniques (NICE 2013b).

In 2013, NHS England commissioned a Commissioning through Evaluation (CtE) programme (National Institute of Health and Care Excellence, 2017) to generate

further evidence about the impact of SIRT on overall survival in chemotherapy refractory or intolerant unresectable primary ICC.

4 Definitions

Best supportive care – is care which aims to prevent or treat as early as possible the symptoms of a disease and the side effects caused by treatment of a disease. It also aims to maintain psychological and emotional wellbeing. It is sometimes also call palliative treatment.

Cancer – are abnormal cells that divide in an uncontrolled way and can spread elsewhere in the body.

Chemotherapy – is a type of systemic therapy involving the use of medicines to kill the cancer cells. There are many different types of chemotherapy medicines and they all work in a similar way by stopping cancer cells reproducing, which prevents them from growing and spreading in the body. Chemotherapy also affects healthy cells and this can cause side-effects, which will vary depending on the type of cell affected.

Liver-specific progression free survival – the length of time from start of treatment to when the disease gets worse in the liver or death.

Metastasis (or secondary tumour) – the term used if the cancer has spread to other parts of the body.

Overall survival (OS) – the length of time from either diagnosis or start of treatment that the patient is still alive.

Performance status - a recognised system developed by the World Health Organisation and other bodies to describe the general health and daily activity status of patients.

Primary cancer or tumour - is the term used for where in the body that a cancer starts.

Progression free survival (PFS) – the length of time from start of treatment to when the disease gets worse or death.

Radiotherapy - is the safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.

Selective internal radiation therapy (SIRT) – the use of microspheres containing a radioactive substance to deliver a targeted dose of radiation to a tumour in order to destroy it.

Systemic therapy – are treatments for cancer using substances that travel through the blood stream to reach and affect cells all over the body. Chemotherapy, immunotherapy and targeted agents are types of systemic therapy.

Time to liver progression – the length of time from start of treatment to when the disease gets worse in the liver. It does not include deaths.

Time to progression (TTP) – the length of time from start of treatment to when the disease gets worse. It does not include deaths.

5 Aims and Objectives

This policy proposition considered the role of SIRT using yttrium-90 microspheres (glass or resin) microspheres as part of the treatment pathway for adults with chemotherapy refractory or chemotherapy intolerant unresectable, primary intrahepatic cholangiocarcinoma.

The objectives were, via evidence review to establish:

1. The evidence on clinical effectiveness of using SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma

who are chemotherapy-refractory or chemotherapy-intolerant, using:

   a) glass yttrium-90 microspheres; and

   b) resin yttrium-90 microspheres.

2. The evidence relating to the safety of SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant, using:

   a) glass yttrium-90 microspheres; and

   b) resin yttrium-90 microspheres.

3. The evidence on the cost effectiveness of SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant, using:

   a) glass yttrium-90 microspheres; and

   b) resin yttrium-90 microspheres.

4. Whether the evidence of clinical and cost-effectiveness identifies any subgroups of patients with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using SIRT with yttrium-90 microspheres compared with best supportive care.

6 Epidemiology and Needs Assessment

ICC is a rare primary liver cancer which arises from the epithelial cells of the bile ducts. ICCs can originate from either small intrahepatic ducts (peripheral cholangiocarcinomas) or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. The majority of cholangiocarcinomas (>90%) are adenocarcinomas and squamous cell carcinoma comprise most of the remaining

cases.

Approximately 1,900 people in the UK are diagnosed with ICC each year, the majority (>65%) of these cases are diagnosed at a stage where the cancer is unresectable.

The 5 year survival rate for resectable ICC is between 20 and 40%; the 5 year survival rate for metastasised unresectable ICC is approximately 2% (Cancer Research UK 2015).

Risk factors for bile duct cancer include primary sclerosing cholangitis, bile duct abnormalities (e.g. fibropolycystic liver disease), biliary stones (hepatolithiasis), chronic liver disease (cirrhosis and viral infection), infection with a liver fluke parasite, exposure to certain chemicals and toxins (e.g. Thorotrast) (NHS Choices 2016a). Rates of ICC have been rising in Western countries which may be explained by factors such as improved detection and diagnosis, misclassification, migration, increasing burden of chronic liver disease, and the potential role of environmental toxins (Valle et al 2016).

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposition for the routine commissioning of this treatment for this indication (chemotherapy refractory or chemotherapy intolerant unresectable, primary intrahepatic cholangiocarcinoma, all ages). An evidence review was undertaken to assess the clinical effectiveness, cost effectiveness and safety of the available SIRT technologies. A Commissioning through Evaluation (CtE) project was also used to assess this technology.

Evidence Review

The evidence review did not identify any studies which compared SIRT with yttrium-90 microspheres to best supportive care in patients with unresectable, chemotherapy-refractory intrahepatic cholangiocarcinoma (ICC).

As there were no comparative studies, three non-comparative, retrospective, case series with a total of 113 patients with advanced or unresectable ICC were included to provide some context on the efficacy of SIRT in this population (Hoffman et al. 2012; Beuzit et al. 2016; Paprottka et al. 2017). Patients in Hoffman et al. (2012). Beuzit et al. 2016; Paprottka et al. 2017). Patients in Hoffman et al. (2012) and Paprottka et al. (2017) were treated with SIRT using yttrium-90 resin microspheres (SIR-spheres), whereas those in Beuzit et al. (2016) were treated using glass microspheres (TheraSphere). The majority of patients in Hoffman et al. and Beuzit et al. had received prior chemotherapy (79% and 91%, respectively), Paprottka et al. did not report this. Therefore some chemotherapy-naïve patients have been included in this review.

These three studies reported median overall survival for patients with ICC treated with SIRT: 22, 19, and 14 months, respectively. Hoffman et al. (2012) reported a median time to progression (TTP) for patients with ICC treated with SIRT of 9.8 months (neither TTP nor progression-free survival (PFS) were reported by the other 2 studies).

Adverse events (AEs) were poorly reported in all 3 studies. Hoffman et al. (2012) stated that no clinically relevant acute toxicities occurred and there were no cases of radiation induced liver disease (RILD). Beuzit et al. (2016) reported that one patient had a severe toxicity event of hepatic encephalopathy. AEs were not reported in Paprottka et al. (2017).

Quality of life outcomes were not reported in the included studies.
All three studies are of limited quality and at risk of bias. The non-comparative nature of their design means that they do not provide relevant evidence on the clinical-effectiveness or safety of SIRT with yttrium-90 compared to BSC in patients with unresectable, chemotherapy-refractory ICC.

No studies were identified which reported the cost-effectiveness of SIRT with yttrium-90 in this ICC population.

Evidence review questions:

1. What is the evidence on clinical effectiveness of using SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant?
   a) glass yttrium-90 microspheres;

None. No comparative studies were identified in this population. One selected non-comparative study reported OS for patients treated with yttrium-90 SIRT glass microspheres.

   b) resin yttrium-90 microspheres.

None. No comparative studies were identified in this population. Two selected non-comparative studies reported OS for patients treated with yttrium-90 SIRT resin microspheres.

2. What is the evidence relating to the safety of SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

   a) glass yttrium-90 microspheres;

None. No comparative studies were identified in this population. Selected non-comparative studies did not adequately report adverse events.

   b) resin yttrium-90 microspheres

None. No comparative studies were identified in this population. Selected non-comparative studies did not adequately report adverse events.

3. What is the evidence on the cost effectiveness of SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

    a) glass yttrium-90 microspheres;

None. No cost-effectiveness studies were identified for this population.

    b) resin yttrium-90 microspheres.

None. No cost-effectiveness studies were identified for this population.

4. Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-only or liver-dominant intrahepatic cholangiocarcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using SIRT with yttrium-90 microspheres compared with best supportive care?

No. No comparative studies were identified in this population.

Higher quality comparative studies exploring outcomes of interest are required to address these questions.

Conclusion

This review provides limited evidence on the clinical- and cost-effectiveness of SIRT with yttrium-90 for the treatment of unresectable, chemotherapy-refractory ICC due to a paucity of high quality comparative studies. Furthermore, the available evidence did not provide any relevant evidence on the safety of this technology in this population. Future studies must include a control group using best supportive care, and report data on adverse events.

CtE SIRT project

The objective of the project was to evaluate the clinical and cost-effectiveness of SIRT in patients with unresectable primary ICC which has progressed following at least one previous chemotherapy line. The single-arm SIRT CtE registry study was carried out in 10 NHS centres in England between December 2013 and March 2017. Data on patients' baseline characteristics, the SIRT procedure, safety, survival, health-related quality of life were collected in a registry. Patients were followed-up for a median of 14.3 months (95% confidence intervals 9.2-19.4).

A total of 61 patients with intrahepatic cholangiocarcinoma treated with SIRT were included in the analysis. 91% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and 81% of patients received 1 or 2 lines of chemotherapy prior to SIRT. Patients required a hospital stay of 1 or 2 nights for the SIRT procedure.

Median overall survival was 8.7 months (95% CIs 5.3-12.1) and survival at 12 months following SIRT was 37%. Median progression-free survival was 2.8 months (95% CIs 2.6-3.1) and median liver-specific progression-free survival was 3.1 months (95% CIs 1.3-4.8).

Changes in EQ-5D-5L scores and EQ-VAS from baseline to 3 months post SIRT were not statistically significant. There were too few respondents at later time points to carry out a comparison.

One patient (2%) had a severe complication on the day of treatment. During the follow-up period, 49% of patients experienced an adverse event, of which 7% of the events were grade 3 and above (severe). The most frequently reported adverse events were mild fatigue and abdominal pain.

Due to the paucity of evidence it was not possible to carry out cost-effectiveness modelling.

8 Documents That Have Informed This Policy Proposition

- Policy Statement: Selective Internal Radiotherapy (SIRT) (reference: B01/PS/a). It is important to note that this policy statement will lapse on publication by NHS England of a clinical commissioning policy for the proposed intervention; and
- Selective Internal Radiotherapy Service Specification (NHS England, 2014).

9 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

10 References

Beuzit, L., Edeline, J., Brun, V., Ronot, M., Guillygomarc'h, A., Boudjema, K., Gandon, Y., Garin, E. and Rolland, Y., 2016. Comparison of Choi criteria and Response Evaluation Criteria in Solid Tumors (RECIST) for intrahepatic cholangiocarcinoma treated with glass-microspheres Yttrium-90 selective internal radiation therapy (SIRT). *European journal of radiology*, *85*(8), pp.1445-1452.

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