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ORIGINAL RESEARCH

Advances in Delivery of Selective Internal Radiation Therapy (SIRT): Economic and Logistical Effects of Same-Stay Work-Up and Procedure in the Treatment of Unresectable Liver Tumors in England

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ABSTRACT

Introduction: Selective internal radiation therapy (SIRT) is a targeted method of treatment for unresectable liver tumors in which radiation therapy is directly delivered to the tumor(s) via the hepatic vasculature. Successful outcomes with SIRT are dependent on the specific vasculature of the liver and tumor, and the patient therefore needs to attend a "work-up" to map the hepatic vasculature prior to the SIRT procedure. Recent advances in SIRT delivery have enabled same-day or same-stay work-up and procedure, requiring only one hospital visit rather than two. We aimed to evaluate the economic, travel time, and transport-related environmental impact of a new brachytherapy device delivery program, the order-map-treat (OMT) program, in patients with unresectable hepatocellular carcinoma (HCC) in England.

Methods: A healthcare resource group (HRG)-based analysis of costs from a national payer (Department of Health and Social Care, DHSC) perspective was conducted assuming that, with OMT, patients would have to attend hospital only once for both the SIRT work-up and procedure versus twice without OMT. Patient travel time and CO_2 emissions were then estimated by identifying the SIRT center closest to the centroid of each clinical commissioning group (CCG) and calculating straight-line distances with a "detour index" to capture the effect of indirect routes via road or rail.

Results: It was estimated that 856 patients per annum would be eligible for SIRT treatment for unresectable HCC in England. OMT would be anticipated to save GBP 2842 per patient versus performing SIRT without OMT. Furthermore, across all patients with HCC eligible for SIRT in England, OMT would avoid 74,500 km of travel, 2299 h of travel time, and 13.9 metric tons of patient transport-related CO_2 emissions annually.

Conclusion: OMT reduces the number of hospital visits required for SIRT by 50%, resulting in financial savings from the DHSC perspective, time savings from the patient perspective, and reduced CO_2 emissions arising from patient transport.

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Key Summary Points

Selective internal radiation therapy (SIRT) is a method of treating unresectable liver tumors in which brachytherapy is delivered directly to the tumor(s) via the hepatic arterial vasculature.

Before the procedure, SIRT requires a work-up to map the hepatic vasculature, typically taking between 60 and 120 minutes, and consisting of a hepatic angiogram and technetium-99m macroaggregated albumin lung perfusion scan.

The order-map-treat (OMT) program is a recent advance in SIRT delivery that has enabled the work-up to take place on the same day or during the same hospital stay as the SIRT procedure.

The present England-focussed analysis showed that, when compared with performing SIRT without OMT, OMT would result in appreciable reductions in costs from the perspective of the Department of Health and Social Care, in addition to reductions in patient travel time and CO_2 emissions arising from patient transportation.

The economic, logistical, and environmental characteristics of SIRT with OMT should be considered by payers, commissioners, and clinicians when selecting the optimal treatment for SIRT-eligible patients with HCC.

INTRODUCTION

Selective internal radiation therapy (SIRT) is a targeted method of treatment for unresectable liver tumors in which brachytherapy is directly delivered to the tumor(s) via the hepatic arterial vasculature. The targeted nature of the therapy is enabled in part by the dual blood supply of the liver; the liver parenchyma receives approximately 75% of its blood supply from the portal vein, while liver tumors typically receive more than 80% of their blood supply through the hepatic artery. Additionally, the microvascular density of liver tumors is much greater than that of the surrounding liver parenchyma. These differences are exploited in transarterial embolization (in which the blood supply to the tumor is intentionally obstructed), in transarterial chemoembolization (in which high-dose chemotherapeutic agents are injected into the tumoral blood supply), and in SIRT (in which the tumor is internally irradiated). In SIRT, radioactive microspheres are infused via the hepatic artery, through which they travel to the tumor, lodging in the tumor vascular bed.

SIR-Spheres® yttrium-90 (Y-90) resin microspheres, a SIRT technology, received a CE mark as an Active Implantable Medical Device in 2002. SIR-Spheres Y-90 resin microspheres provide localized radiotherapy from Y-90, a beta emitter with a half-life of 64.1 h and a mean emission range of 2.5 mm [1, 2]. In England and the European Union, SIR-Spheres Y-90 resin microspheres are used for the treatment of unresectable hepatocellular carcinoma (HCC), as well as for the treatment of unresectable chemotherapy-refractory metastases from colorectal cancer (mCRC) [3, 4]. SIRT is included in guidelines for the management of these conditions [5–9]. The goals of SIRT are to increase the time to disease progression, extend overall survival, and/or provide palliation of symptoms in patients with either primary or secondary liver tumors. In patients with unresectable HCC, SIRT may also be used to downstage to potentially curative therapy such as resection or liver transplantation [10–13]. Using SIRT to downsize and bridge to curative therapies is also possible in patients with mCRC [14].

Given the heavy reliance of SIRT on the specific vasculature of the liver and tumor, the use of SIR-Spheres Y-90 resin microspheres requires the patient to attend a "work-up" prior to the SIRT procedure. The work-up, which

typically takes from 60 to 120 minutes, consists of a hepatic angiogram, scintigraphy (also known as a lung-shunting scan or macroaggregated albumin [MAA] lung perfusion scan), and potentially also a computed tomography (CT)–hepatic angiogram, which can provide a detailed picture of the hepatic arterial architecture. The scintigraphy utilizes the radiotracer technetium-99 m (^{99m}Tc), which is bound to MAA particles, allowing the blood flow from the hepatic artery to the lung to be observed using single photon emission computed tomography (SPECT) or combined SPECT/CT. If required, a CT–hepatic angiogram provides further information on the anatomy of the liver blood vessels. The results of the work-up can disqualify certain patients from SIRT; for example, the procedure is contraindicated if the ^{99m}Tc-MAA scan demonstrates a lung shunt fraction of 20% or more, or if the pre-assessment angiogram demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas, or bowel [3]. Conventionally, following work-up, if the decision is made to proceed with the SIRT procedure, an order is placed and the SIR-Spheres Y-90 resin microspheres are produced and shipped to the medical facility [15]. The work-up and SIRT procedure are therefore carried out as separate elective stays, with the average interval between them being from 1 to 4 weeks. However, the gap between work-up and the SIRT procedure increases the likelihood that the procedure will not be able to take place because of disease progression; excessive delays increase the likelihood of deterioration in performance status and/or liver function. Likewise, longer intervals between work-up and the SIRT procedure increase the chance of changes to liver vasculature occurring between work-up and administration of SIR-Spheres Y-90 resin microspheres, potentially precluding patients from ultimately receiving SIRT [15]. There are therefore clear benefits to performing work-up and the SIRT procedure on the same day or during the same hospital stay. Such an approach could potentially deliver greater treatment effectiveness by limiting disease progression, reducing interruptions between treatments, and supporting the continuum of care. Additional patient benefits may include a reduced time to treatment, reduced recovery time, and fewer hospital visits [16].

With SIR-Spheres Y-90 resin microspheres, the order-map-treat (OMT) program was designed with these potential benefits in mind, enabling the work-up ("map") and SIRT procedure ("treat") to be performed during the same stay, and possibly on the same day [17–19]. This ability to perform the work-up and SIRT procedure during the same hospital stay with OMT is beneficial as it has the potential to require only one hospital admission for each SIRT treatment, possibly as a day-case, thereby mitigating the aforementioned risk of disease progression in the time between the work-up and SIRT procedure. In the SARAH randomized controlled trial of SIR-Spheres Y-90 resin microspheres versus sorafenib, for example, the median delay between randomization and treatment initiation was 29 days (interquartile range [IQR] 23–36) in the SIRT group versus 7 days (IQR 3–9) in the sorafenib group, with the difference at least in part attributable to the need for patients to undergo work-up ahead of the SIRT procedure itself [20]. Furthermore, in both the SARAH and SIRveNIB trials, more patients did not ultimately receive the assigned treatment in the SIRT group versus the sorafenib group, resulting in differences in outcomes between the intent-to-treat and per protocol analyses [20–22].

In the present study, we aimed to conduct an economic analysis to investigate the costs, patient travel time, and environmental implications of OMT compared to the current pattern of SIRT treatment without OMT. Furthermore, we place these findings in the context of other recent developments in SIRT, including transradial versus transfemoral access, and more flexible delivery options for SIRT products.

METHODS

Estimation of Patients with Hepatocellular Carcinoma Eligible for Selective Internal Radiation Therapy

A top-down approach was employed to estimate the annual number of patients with HCC who

would be eligible for SIRT annually in England, according to the National Institute of Health and Care Excellence (NICE) recommendations made in Technology Appraisal 688 [23]. Patients with HCC were selected as the target population in line with the NICE multiple technology appraisal (MTA) of SIRT, which specifically evaluated SIRT technologies in people with unresectable early (BCLC stage A), intermediate (BCLC stage B), and advanced (BCLC stage C) HCC with or without portal vein thrombosis/involvement [23]. An incidence-based patient flow model was constructed on the basis of a resource impact template developed by NICE as part of the MTA of SIRT in the treatment of HCC (Fig. 1) [23–27]. A full description of the data sources used in each step of the flow model is provided in the Supplementary Material.

Economic Analysis of the Order-Map-Treat Program

The effects of OMT on direct healthcare costs were evaluated from the perspective of the Department of Health and Social Care (DHSC), the national healthcare payer in England. Costs of work-up and treatment were calculated using the 2022–23 National Tariff incorporating the July 2022 cost uplift factor, and the cost reduction was assumed to arise from the avoidance of one hospital spell for the pre-treatment work-up (Table 1 and Fig. 2). In both scenarios (with and without OMT), the cost of treatment was calculated assuming an average of 1.11 SIRT treatments per patient—with each treatment comprising one work-up and one SIRT procedure—in line with the assumptions in the NICE resource impact template that accompanied the MTA (Table 1) [23].

In the scenario without OMT, each administration was associated with the cost of the SIR-Spheres Y-90 resin microspheres, a pre-treatment work-up cost calculated using a weighted average of elective healthcare resource group (HRG) codes YR54A-C ("Percutaneous Transluminal Embolisation of Peripheral Blood Vessel"), and two HRG codes covering the SIRT procedure: YR57Z ("Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver") and SC28Z ("Deliver a Fraction of Interstitial Radiotherapy"; Table 1). These HRG codes were derived de novo using the HRG4 + 2022–23 Local Payment Grouper to align with the HRG codes used in the NICE resource impact template [28]. Specifically, the HRG codes for the SIRT procedure were derived using a diagnosis of liver cell carcinoma (ICD-10 code C22.0) combined with OPCS-4 procedure codes for SIRT as recommended in the 2022 National Clinical Coding Standards (Supplementary Material Fig. 1) [29]. The OPCS-4 procedure code for the SIRT work-up (J10.1 or "Percutaneous transluminal embolisation of hepatic artery") was determined from the Local Payment Grouper using informed trial and error to match the HRG code used in the NICE resource impact template (YR54A-C).

In the scenario with OMT, the OPCS-4 codes for the work-up and SIRT procedure were added to a single spell to establish the dominant procedure (and therefore the dominant HRG code), as under the current National Tariff Payment System only a single core HRG code can be assigned to each hospital spell. This was the key driver of the cost difference from the DHSC perspective; without OMT, the work-up would be conducted during a separate hospital spell and would be assigned to the patient record in addition to the SIRT procedure spell. The SC28Z HRG code, included in costings of the SIRT procedure regardless of whether OMT is used, is an "unbundled" HRG, and was therefore assigned alongside the core HRG in the spell during which the SIRT procedure was performed. As SC28Z has no price published in the 2022–23 National Tariff, the price was taken from the National Schedule of NHS Costs 2019/20 in line with advice from the National Casemix Office [30].

As the analysis was conducted at the national level and focused primarily on establishing a relative cost with OMT versus without, the average market forces factor (MFF) across all NHS England providers of 1.067 was applied to the underlying tariff costs. The MFF is otherwise a means of adjusting NHS resource allocation to capture unavoidable cost differences between healthcare providers in different parts of the

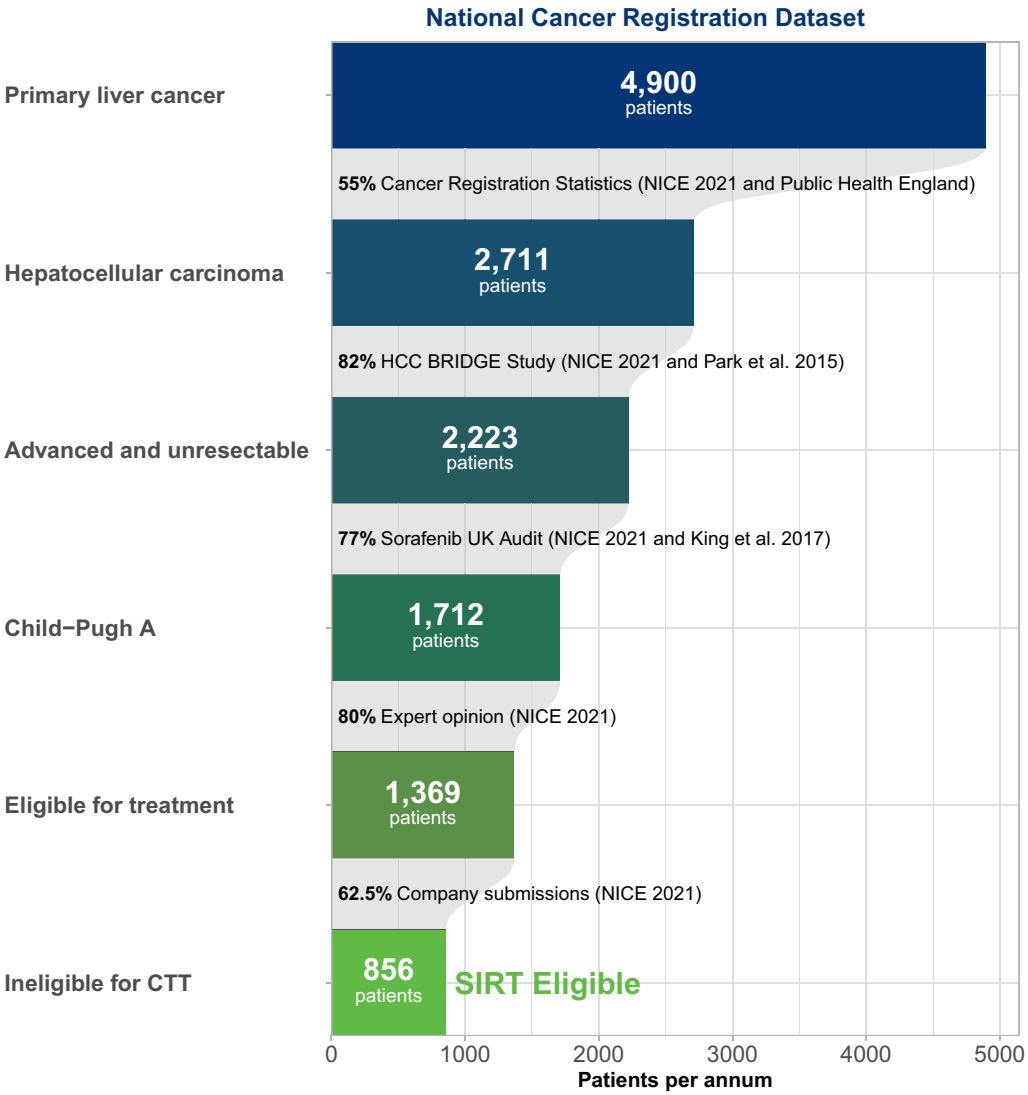

Fig. 1 Flow diagram showing patient selection criteria for selective internal radiation therapy in line with the NICE multiple technology appraisal of selective internal radiation therapies in the treatment of hepatocellular carcinoma. *CTT* conventional transarterial therapies, *HCC* hepatocellular carcinoma, *NICE* National Institute for Health and Care Excellence, *SIRT* selective internal radiation therapy

country [31]. The cost of a dose of SIR-Spheres Y-90 resin microspheres was taken from the public manufacturer list price, as reported in the recent MTA of SIRT technologies in the treatment of unresectable HCC conducted by NICE [23]. SIR-Spheres Y-90 resin microspheres are subject to a patient access scheme (PAS), which reduces the cost borne by the provider, but the details of the scheme are confidential and the effect of the PAS was therefore excluded.

Patient Travel Time and CO_2 Emissions Analysis of the Order-Map-Treat Program

A patient travel time model was developed for NHS England, using a Clinical Commissioning Group (CCG)-based model of patient travel. Prior to the introduction of Integrated Care Systems in July 2022, CCGs were local NHS organizations responsible for commissioning the majority of healthcare services; originally

Table 1 Unit costs used in the economic analysis

	HRG code	Number of treatment cycles per patient	Cost per treatment (GBP)	Total cost of treatment (GBP)	Total cost of treatment including MFF (GBP)
Pre-treatment work-up	YR54A-C	1.1	2399	2663	2842
Percutaneous, chemoembolization or radioembolization, of lesion of liver	YR57Z	1.1	3865	4290	4578
Deliver a fraction of interstitial radiotherapy*	SC28Z	1.1	2188	2428	2428
SIR-Spheres Y-90 resin microspheres	–	1.1	9600	10,656	10,656

GBP pounds sterling, *HRG* healthcare resource group, *MFF* market forces factor
*Based on 2019/20 NHS Reference Costs, multiplied by the increase in the YR57Z tariff between 2019/20 and 2022/23 (without applying an MFF as the base cost was a retrospectively calculated reference cost)

there were over 200 CCGs with each commissioning care for a median of 226,000 people [32]. For each CCG, the geographical boundary of the CCG was retrieved from the Office for National Statistics Open Geography Portal, and the centroid (an arithmetic mean of the points defining the boundary) of each CCG was calculated [33]. The original CCG boundaries were used as the basis of the analysis as they provide a higher degree of geospatial resolution than the Integrated Care Systems and therefore improve the accuracy of the transportation modeling. A list of active SIRT centers was obtained from a recent All-Party Parliamentary Group report on Barriers to Patient Access of Minimally Invasive Cancer Therapies (Table 2) [34]. The average distance from the centroid of each CCG to the nearest of the ten centers in England performing SIRT using SIR-Spheres Y-90 resin microspheres was then calculated (Fig. 3). As the underlying distances were calculated using the haversine formula (and therefore represented the shortest possible spherical distance between the CCG centroid and the nearest SIRT center), the model used a detour index to capture the indirect nature of journeys taken by road or rail [35]. The detour index was sourced from a 2012 US study comparing driving distance with straight-line travel distances to US hospitals [35]. After adjustment using the detour index, this average distance was assumed to represent the average distance that a patient would need to travel from each CCG; implicit in this CCG centroid-based model was the assumption of an evenly distributed population across each CCG.

A transportation mix was then layered onto the mean distance calculations based on 2019 national data from the Department of Transport (the last year for which data were available prior to the COVID-19 pandemic), specifically assigning the proportion of trips taken by private versus public transport at a ratio of 580:33 trips [36]. The analysis was then conducted using the simplifying assumption that private transportation would be by car and public transportation would be by train, with respective average travel speeds of 45 km/h and 60 km/h over the whole journey. Mean CO_2 emissions per kilometer by transport modality (142 g/km by car and 14 g/km by train) were also obtained from the Department of Transport and applied to the transport split [37].

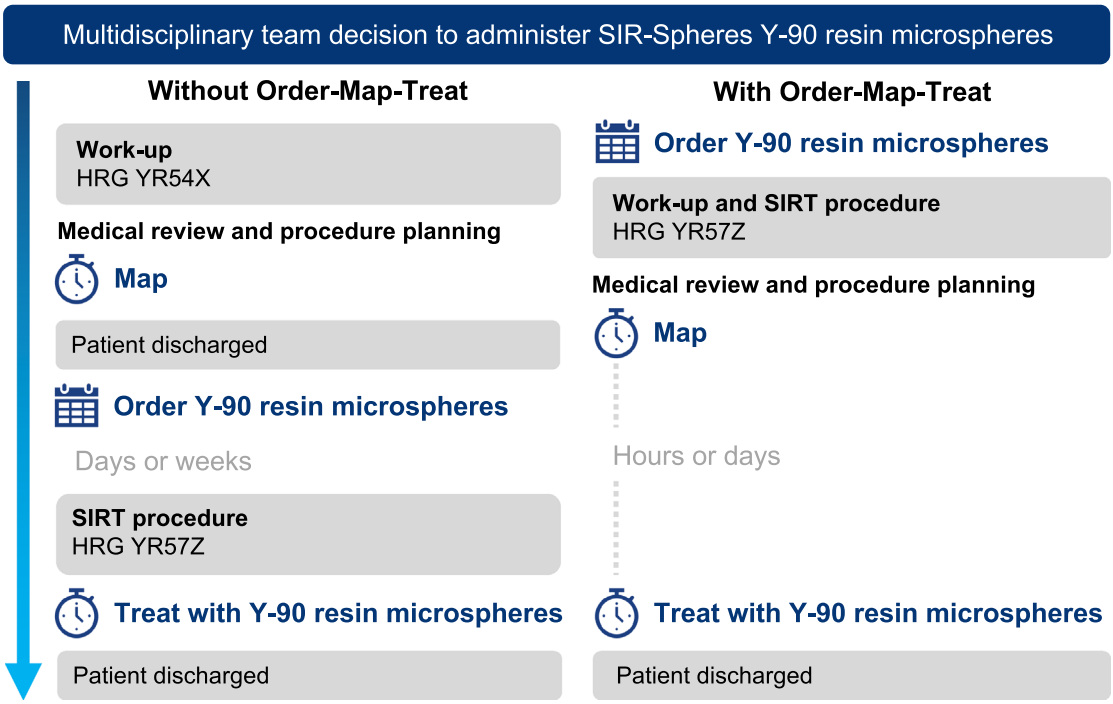

Fig. 2 Selective internal radiation therapy work-up and procedure with and without the order-map-treat program. *HRG* healthcare resource group, *SIRT* selective internal radiation therapy, *Y-90* yttrium-90

For the comparison of distance, time, and CO_2 emissions from patient transportation between SIRT using SIR-Spheres Y-90 resin microspheres with and without OMT, it was assumed that OMT would result in a single hospital trip per treatment with SIR-Spheres Y-90 resin microspheres versus two trips without OMT.

RESULTS

Estimation of Patients with Hepatocellular Carcinoma Eligible for Selective Internal Radiation Therapy

The top-down calculation of patients eligible for SIRT in line with the NICE recommendation yielded an estimate of 856 patients: with an annual incidence of 2711 patients with HCC, 2223 have advanced and unresectable disease, 1712 have Child–Pugh grade A liver function, 1369 would be eligible for treatment, and 856 would not be eligible for conventional transarterial therapies and therefore would be eligible for SIRT. This value was aligned with the estimate in the NICE resource impact template [23]. With the average of 1.11 SIRT treatments per patient would result in 950 work-ups and SIRT procedures being performed per year.

Economic Analysis of the Order-Map-Treat Program

Because OMT enables work-up and SIRT procedure to be performed in a single stay, the cost savings from the national payer perspective relative to administering SIR-Spheres Y-90 resin microspheres without OMT would be GBP 2842 per patient, corresponding to a cost reduction of 13.9% from GBP 20,504 to GBP 17,663 per patient (Fig. 4). If the entire population eligible for treatment with SIRT were treated with SIR-Spheres Y-90 resin microspheres, SIRT with OMT would result in annual savings of GBP 2.4 million relative to SIRT without OMT across NHS England, reducing costs from

Table 2 Active SIRT centers captured in the patient travel time analysis

Hospital name	Location	NHS trust
Churchill Hospital	Oxford	Oxford University Hospitals NHS Foundation Trust
Christie Hospital	Manchester	Christie NHS Foundation Trust
Royal Free Hospital	London	Royal Free London NHS Foundation Trust
Nottingham City Hospital	Nottingham	Nottingham University Hospitals NHS Trust
Freeman Hospital	Newcastle	Newcastle upon Tyne Hospitals NHS Foundation Trust
Southampton General Hospital	Southampton	University Hospital Southampton NHS Foundation Trust
Addenbrooke's Hospital	Cambridge	Cambridge University Hospitals NHS Foundation Trust
Queen Elizabeth Hospital	Birmingham	University Hospitals Birmingham NHS Foundation Trust
King's College Hospital	London	King's College Hospital NHS Foundation Trust
St James's Hospital	Leeds	Leeds Teaching Hospitals NHS Trust

GBP 17.6 million to GBP 15.1 million per annum.

Patient Travel Time and CO_2 Emissions Analysis of the Order-Map-Treat Program

The patient travel time analysis showed that, across the 950 annual SIRT treatments, OMT would be anticipated to reduce the number of hospital visits in NHS England by 950 visits annually, reducing patient travel distance by 74,530 km per annum, saving 2299 h of patient time and reducing travel-related CO_2 emissions by approximately 13.9 metric tons per annum (Table 3).

DISCUSSION

The present analysis showed that OMT would be anticipated to reduce the number of patient contacts with the health service by up to 950 visits annually, resulting in a reduction of 74,530 km travelled by patients to access SIRT services, corresponding to reductions of 2299 h of travel time and 13.9 metric tons of CO_2 arising from patient transportation.

The analysis focused exclusively on patients with unresectable HCC eligible for treatment with SIRT, and furthermore assumed that all the eligible patients would be treated with SIRT. The estimates presented therefore represent the maximum possible monetary, time, and CO_2 emissions savings that could be achieved annually with OMT in patients with HCC in England. While these maximum estimates would likely be lower in routine clinical practice as a result of patient ineligibility for OMT, use of other SIRT and locoregional technologies, or systemic agents such as atezolizumab-bevacizumab, sorafenib, lenvatinib, and regorafenib, the present analysis may still represent an underestimate of the savings from OMT in total, owing to the exclusion of other indications that are commonly treated with SIRT using SIR-Spheres Y-90 resin microspheres such as mCRC [38–41]. Furthermore, the present analysis only compared SIRT without OMT and SIRT with OMT. Comparisons with other treatment modalities may yield much greater estimates of travel time and transport-related CO_2 emission reductions; for instance, the NICE resource impact template for SIRT in the treatment of HCC notes that, on average, patients with HCC treated with sorafenib receive 5.78 cycles of treatment, while patients treated with lenvatinib receive 9 cycles of treatment. The corresponding resource impact template for atezolizumab-bevacizumab in the treatment of HCC reports that patients would receive 19 cycles of treatment with atezolizumab, which is

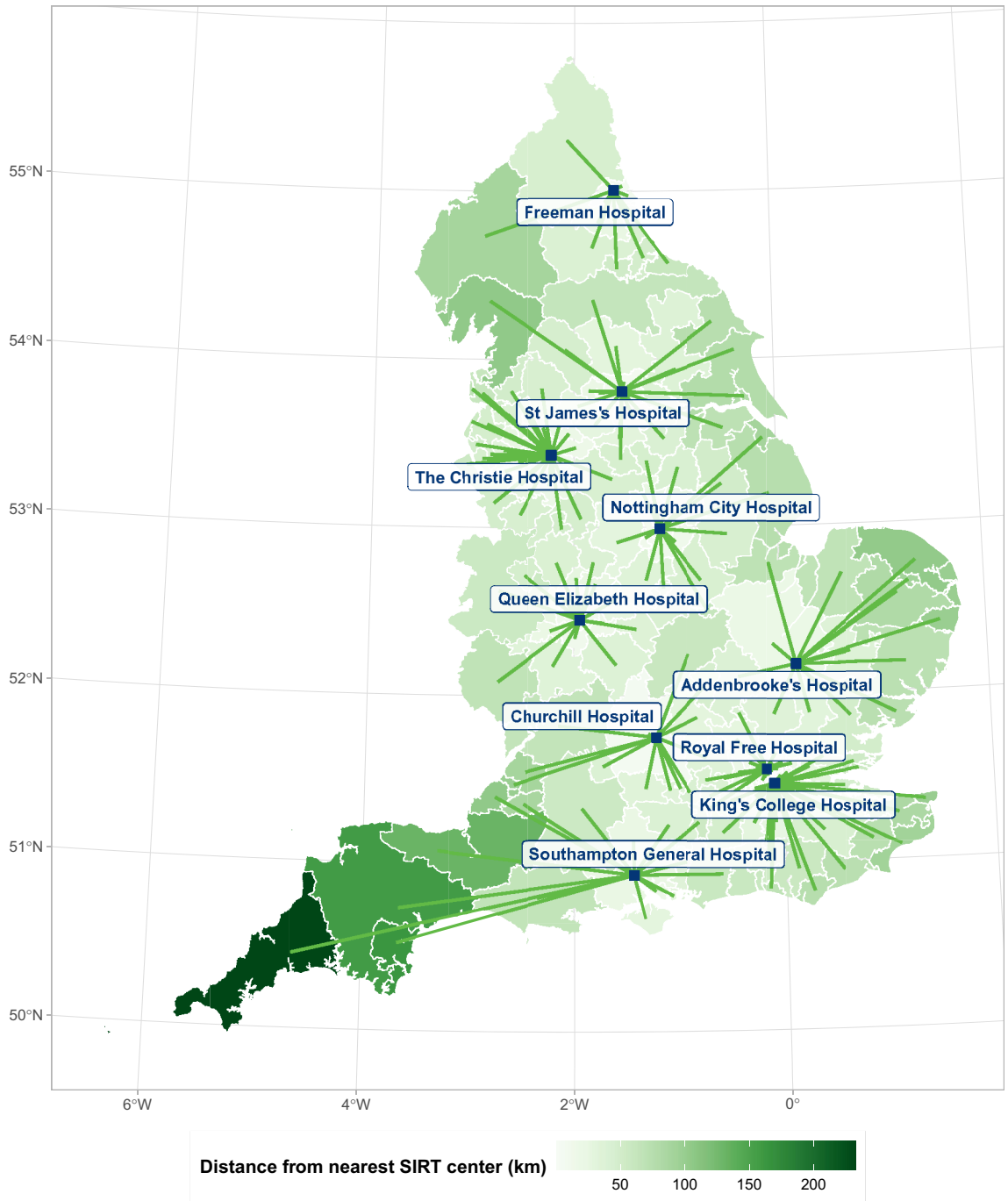

Fig. 3 Patient travel distance model showing each active SIRT center connected to the centroids of the clinical commissioning groups nearest to the SIRT center. Source: Office for National Statistics licensed under the Open Government Licence v.3.0. Contains OS data © Crown copyright and database right 2022

administered by intravenous infusion and therefore much less likely to be prescribed/administered opportunistically at other diagnostic appointments. While the hospitals able to dispense oral chemotherapy agents or administer intravenous therapies are far more numerous

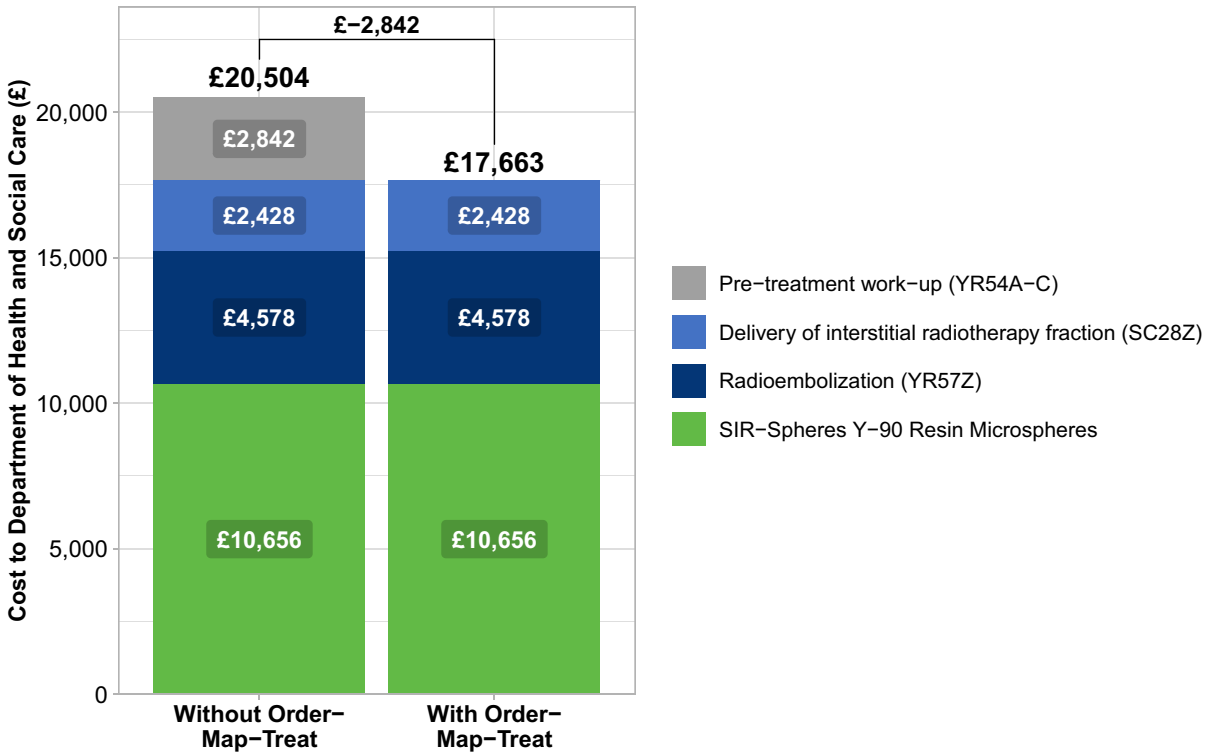

Fig. 4 Overall, per-patient, healthcare resource group-based cost estimates of SIR-Spheres Y-90 resin microspheres, work-up, and selective internal radiation therapy procedure with and without the order-map-treat program

than centers able to perform SIRT (and therefore on average closer to patients), attending the hospital even just once per treatment cycle places a substantial additional burden on the patient versus an average of 1.11 hospital admissions for SIRT.

The present analysis showed that OMT results in economic benefits from the payer perspective relative to SIRT without OMT; the analysis did not specifically investigate the implications from a healthcare provider perspective, but SIRT with OMT would be anticipated to provide advantages in terms of reducing healthcare utilization burden relative to a SIRT procedure without OMT. Indeed, SIRT with OMT requires less hospital staff time and can be performed as a day-case procedure, resulting in a reduction in hospital bed utilization, freeing both beds and staff time for other hospital activities and procedures. Relatedly, a recent review of molecular radiotherapy services in the UK showed that access to molecular radiotherapy treatments is heterogeneous across the UK [42]. The disparities were attributed to lack of trained staff, lack of physical facilities, and variations in NHS reimbursement for these treatments in different parts of the UK. By providing a clear treatment protocol and the ability to reduce the healthcare utilization burden associated with SIRT, OMT could help to reduce disparities in access to radiotherapy services.

In addition to the tangible benefits of reducing costs, travel time, and transport-related CO_2 emissions, the benefits of reducing unnecessary contacts with the healthcare system have become more apparent during the COVID-19 pandemic, reducing the opportunity for spread of infection. Despite ongoing reductions in the prevalence of COVID-19 in the UK, reducing unnecessary contacts with the healthcare system is still beneficial in terms of reducing the transmission rate of COVID-19, other airborne diseases, and nosocomial infections more broadly. In this context, SIRT is a flexible and well-tolerated treatment, allowing tumor progression to be controlled (or tumor

Table 3 Distance, travel time and CO_2 emissions estimates in patients with hepatocellular carcinoma in England treated with selective internal radiation therapy with and without the order-map-treat program

	Per SIRT procedure	Annually across all procedures for HCC
Distance travelled to SIRT centers		
Average round-trip without OMT (km)	156.89	149,071
Average round-trip with OMT (km)	78.44	74,531
Round-trip distance saving with OMT (km)	78.44	74,531
Travel time to SIRT centers		
Average travel time without OMT (h)	4.84	4599
Average travel time with OMT (h)	2.42	2299
Travel time saving with OMT (h)	2.42	2299
CO_2 emissions from travel to SIRT centers		
Average CO_2 emissions without OMT (kg)	29.25	27,792
Average CO_2 emissions with OMT (kg)	14.62	13,891
CO_2 emissions saving with OMT (kg)	14.62	13,891

HCC hepatocellular carcinoma, *OMT* order-map-treat program, *SIRT* selective internal radiation therapy

load to be reduced) while patients are waiting for evaluation or access to other therapies; such adaptable treatment pathways are particularly beneficial during global health crises such as the COVID-19 pandemic, but are also clearly advantageous in routine practice [43]. OMT increases this aspect by enabling single-stay treatment of HCC, compared to systemic therapies or chemoembolization which generally require several hospitalizations, sometimes lasting multiple days [44, 45]. It is aligned with the recommendation to conduct the SIRT procedure as soon as possible after the work-up [46]. The option of delivering SIRT using Y-90 resin microspheres with same-day discharge (as distinct from same-stay) was an additional benefit for hospitals and patients during the COVID-19 pandemic [18]. Furthermore, a recent report from the National Audit Office highlighted that the pandemic delayed cancer patient diagnosis and treatment access within the NHS [47]. The report raises concerns about the worsening impact on waiting lists in the country. In this context, OMT avoids the additional delay between the work-up and the SIRT procedure for patients, which may be already impacted by waiting lists.

This economic analysis had a number of key strengths, in that it was based on a robust HRG-based costing methodology and was highly transparent in the key underlying assumption of a 50% reduction in the number of hospital appointments required for each SIRT treatment. However, some limitations of the analysis methodology should also be acknowledged and considered when interpreting the findings. One key limitation arose from the lack of robust data on work-up failure rates with and without OMT. It is conceivable that patients attending a same-day or same-stay work-up and SIRT procedure would be found to be ineligible for SIRT and, owing to the same-day or same-stay treatment under OMT, the SIR-Spheres Y-90 resin microspheres would necessarily already be on-site at the nuclear medicine department. OMT could thereby potentially result in additional product wastage that would not occur if the work-up was conducted prior to the product being

ordered; however it is worth noting that the financial risk in this instance is covered entirely by the SIR-Spheres Y-90 resin microspheres manufacturer. The analysis also assumed that all patients with HCC eligible for SIRT would be treated with SIRT with OMT, which may not be realistic.

Other limitations included the use of a detour index to estimate the average distances traveled from each CCG rather than performing the calculation based on real-world routes to the nearest SIRT centers, and the limited modes of transportation modeled in the base case analysis. The former limitation could have been addressed by retrieving average routes from each CCG to the nearest SIRT center from online mapping software; however, this would be expected to have a negligible impact on the findings [35]. The latter limitation, focusing exclusively on ground-based transportation, thereby omitted certain edge-cases in the setting of NHS England including, for example, patients traveling from the Isle of Wight to the nearest SIRT center in Southampton, which would necessarily involve transportation either by boat or air. This limitation could have been addressed by incorporating these less commonly used modes of transportation into the model, but likely with only minimal impact on the travel time and CO_2 emissions estimates given the relatively small proportion of the population within England not living on the mainland. One final limitation is that the transportation and CO_2 emissions estimates are subject to change depending on the number of centers able to perform SIRT in the UK; if the number of SIRT centers increases over time, the effect of OMT on reducing transport time and CO_2 emissions would diminish, although the magnitude of the cost savings from the DHSC perspective would be unaffected.

OMT is predicated on the ability to draw a tailored microsphere dose activity from the delivery vial to yield the appropriate activity for the patient. The ability to draw custom volumes of microspheres from the delivery vial is unique to SIR-Spheres Y-90 resin microspheres, making it well suited to performing same-day or same-stay SIRT. In addition to the ability to draw tailored activities from the delivery vial, the FLEXdose Delivery Program enables even greater treatment flexibility, allowing the prescribed radioactivity to be administered with more or fewer SIR-Spheres Y-90 resin microspheres depending on the targeted treatment area (Supplementary Material Fig. 2). Five different delivery options are possible in Europe, favoring a personalized dosimetry according to various aspects such as the number of tumors, the targeted liver volume, tumor location(s) and aspect, vascular characteristics of the patient, and treatment goal, as recommended in a recent international SIRT expert consensus statement [46]. In practice, this flexibility enables clinicians to optimize treatment according to the patient characteristics, but also to adapt according to real-world constraints such as a treatment delay or the need to adapt SIRT treatment (increasing activity or extending coverage) according to personalized dosimetry parameters brought to attention before and during the procedure. SIRT using personalized dosimetry is now highly recommended, including calculation of dose, activity and coverage necessary to treat each patient (most often via specialized software), and a post-dosimetry assessment of treatment efficacy [46]. The real-life benefits offered by SIR-Spheres Y-90 resin microspheres for patients, clinicians, and health systems as a whole, therefore, are likely to be greater than those presented in this analysis.

The ability to perform SIRT through the radial rather than femoral artery with transradial access (TRA) represents another recent advance in the delivery of SIRT, with TRA resulting in significant reductions in recovery time relative to transfemoral access (TFA) [48], and high rates of success, with conversion from TRA to TFA only required in 2.3% of 574 SIRT procedures in an early study of the transradial approach [49]. Finally, regarding selection of patients for SIRT, a post hoc analysis of data from the SARAH RCT has shown that patients with tumor burden of at most 25% and well-preserved liver function (albumin-bilirubin grade 1) may experience substantial improvements in overall survival [12]. Furthermore, patients with HCC receiving a tumor-absorbed dose greater than 100 Gy have shown significant improvements in OS and disease control

versus patients receiving doses less than 100 Gy, highlighting another clinically relevant advance in the understanding and use of SIRT [46, 50].

CONCLUSION

In aggregate, the improvements in SIRT procurement, the expanded delivery options, and evolving criteria for optimal patient selection result in a SIRT treatment experience that is meaningfully superior in terms of flexibility, patient experience, and potentially also clinical outcomes when compared with SIRT treatments conducted prior to these developments. The additional cost savings arising from OMT also further enhance the economic proposition associated with SIRT; together, these improvements in the economic, logistical, and clinical characteristics of SIRT should be considered by payers, commissioners, and clinicians when selecting optimal treatments for SIRT-eligible patients with HCC.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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