HTA REPORT

Selective Internal Radiation Therapy (SIRT) in colorectal liver metastases

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HTA REPORT

Selective Internal Radiation Therapy (SIRT) in colorectal liver metastases

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Foreword

This year Agenas has produced a HTA report on the use of Selective Internal Radiation Therapy (SIRT) for treatment of colorectal liver metastases on behalf of the Italian Ministry of Health. The HTA report was developed to answer the question: "What is the impact on the Italian NHS of adding radioembolization with ^{90}Y-Microspheres on current treatments for patients with non-resectable liver metastases from primary colorectal cancer (CRC)?".

The latest evidence on clinical effectiveness has been synthesized by a systematic review of literature. To describe the patterns of real use and expected expenditure of SIRT, Agenas carried out a survey involving nineteen Italian Centres which were probably performing SIRT.

The results of the systematic review show that the evidence for the combination of SIRT with chemotherapy vs. chemotherapy alone for the treatment of colorectal liver metastases is limited, notwithstanding the publication in the next few years of large datasets from trials nearing completion. A more rational use of resources would involve concentration of all patients in a smaller number of qualified Hospitals doing higher volumes of SIRT and accruing experience with the technique.

In addition, given the nature and stage of the disease in which patients are candidates for treatment, the cost of SIRT and the uncertainty surrounding its effects, the adoption of SIRT would be recommended in few selected cases.

Fulvio Moirano

Executive Director of Agenas

Prefazione

Quest'anno Agenas ha prodotto, su mandato del Ministero della Salute un report di HTA sull'utilizzo della Selective Internal Radiation Therapy (SIRT) per il trattamento delle metastasi epatiche da carcinoma del colon-retto.

Il report è stato sviluppato a partire dal seguente quesito: "Qual è l'impatto generato sul Sistema Sanitario Italiano se al trattamento corrente (chemioterapia) per metastesi epatiche da carcinoma coloroettale viene aggiunto anche quello di radioembolizzazione con ^{90}Y-Microspheres?".

Le prove di efficacia clinica sono state sintetizzate mediante revisione sistematica della letteratura mentre, per la descrizione dell'utilizzo nel contesto italiano e per il rilevamento dei costi è stata predisposta una survey presso tutti i centri italiani che utilizzano la SIRT.

I risultati suggeriscono che le prove di efficacia dell'utilizzo della SIRT per il trattamento delle metastasi epatiche da carcinoma del colon-retto sono molto limitate, sebbene diversi studi multicentrici siano in corso di svolgimento. Gli elevati costi possono essere contenuti solo mediante l'adozione della SIRT in centri qualificati di alta specializzazione. Inoltre, considerata la natura e lo stadio della malattia in cui si trovano i pazienti candidati al trattamento, i costi della SIRT e l'incertezza che circonda i suoi effetti, l'adozione del trattamento SIRT sarebbe consigliabile in pochissimi e selezionati casi.

Fulvio Moirano

Direttore Generale Agenas

Executive summary

One-liner

We assessed effectiveness, acceptability and costs of the combination of SIRT with chemotherapy vs. chemotherapy alone for the treatment of liver metastases from Colorectal cancer (CRC).

Background

CRC is one of the most frequent cancers in the western world, with a prevalence of 300,000 cases in Italy and 52,000 new diagnoses in 2012. Liver metastases from CRC develop in 50% of patients but only 25% of those are considered to have resectable metastases. The primary aim of treating CRC liver metastases is to decrease the lesions' size and spread. Surgical resection is the treatment of choice for resectable colorectal metastases. For unresectable metastatic disease, systemic medical therapy (chemotherapy) is the first choice treatment, but local therapy such as loco-regional radiotherapy and ablative procedures, may be associated in an attempt to prolong survival or to palliate symptoms (e.g. pain). Radioembolization, also known as Selective Internal Radiation Therapy (SIRT) is a form of intra-arterial brachytherapy used to treat primary liver cancer and liver metastases. The potential benefits of radioembolization technology for CRC liver metastases treatment can be significant in terms of economical and organizational impact and important ethical implications such as patient's expectations and hopes.

Objective

To assess clinical effectiveness, acceptability, costs and organisational aspects of SIRT for the treatment of liver metastases from CRC.

Methods

For clinical effectiveness analysis we carried out a systematic review of literature, including studies on people aged 18-80 with non-resectable liver metastases from primary CRC. The Intervention assessed was SIRT using Yttrium-90 coated microspheres administered via the hepatic artery compared to chemotherapy at 2nd and later lines and excluding supportive therapy.

We carried out a literature search on the following databases: MEDLINE, EMBASE, Cochrane Library, Health Technology Assessment websites, trial registries. We aimed to include HTA reports, systematic reviews and comparative prospective primary studies (trials and cohort studies) carried out from 1997 to date in English or Italian.

Data on study design, study population, SIRT and comparator outcomes were extracted. We assessed studies according to randomization, generation of the allocation sequence, allocation concealment, blinding and follow up. Interpretation of the studies' results was carried out in terms of numerousness, quality and consistency.

We performed a context analysis of the nineteen Italian Centres which were able to perform SIRT for the treatment of liver metastases from CRC. We adopted a questionnaire to collect data and information on diffusion, type of technology and resource used, data on clinical outcomes, patient selection and costs of procedure.

We conducted a systematic review of the italian and international scientific literature to identify and describe the economic evaluation studies of SIRT for liver metastases from primary CRC. We carried out a cost analysis of SIRT technology using data collected from questionnaires.

Finally, we used different sources of information to collect views and hopes of patients who used SIRT.

Results

We included one small open label randomized trial carried out on 46 patients. The study is small and its generalizability is unclear.

In our survey the majority of hospitals provided SIRT in one session. Choice of number of sessions depended on cost and on extension of metastatic disease (unilobar, bilobar), reduction of technical complications potentially related to several sessions, different vascular supply of liver metastases and different response of each metastatic nodule to chemotherapy.

Fifty percent of liver involvement is the highest acceptable threshold in all hospitals. An increasing number of Centers are employing SIRT early (2^{nd} or 3^{rd} line).

Considering the therapeutic potential of SIRT, the impact of SIRT in Italy should be tested with a larger use of prospective studies, similarly to clinical strategies promoted by other countries. Moreover, our survey shows that the number of patient yearly treaded is relatively small with no more than 12 patients treated per year. We calculated the total cost of SIRT procedure by adding the costs of diagnostic work-up, treatment and follow up. The median cost is 15,229 euro ranging from 13,582 to 17,370. The costs of an individual dose of radioisotopes amounts to 10,000 euro.

For the patients being able to undergo radioembolization means having a further chance. The attitude toward it is usually positive and the probable side effects are regarded as tolerable. Any future study comparing radioembolization with other therapies should always include QoL as a secondary outcome measured with standardized and internationally validated instruments.

Recommendations

We recommend that the results of completed and nearly completed trials currently still active, be reported at the earliest opportunity. A national resource optimization plan is needed.

Synthesis

Clinical problem and target population

Colorectal cancer (CRC) is one of the most frequent cancers in the western world, with a prevalence of 300,000 cases in Italy and 52,000 new diagnoses in 2012. Liver metastases from CRC develop in 50% of patients but only 25% of those are considered to have resectable metastases. The five-year survival rate after surgery is 20% to 40%.

The primary aim of treating CRC liver metastases is to decrease the lesions' size and spread. Surgical resection is the treatment of choice for resectable colorectal metastases. However, only 10 to 25 percent of patients with isolated liver metastases are eligible for resection because of anatomical constraints, inadequate hepatic functional reserve or concurrent medical co-morbidities such as poor performance status and cardiac failure. For unresectable metastatic disease, systemic medical therapy (chemotherapy) is the first choice treatment, but local therapy such as loco-regional radiotherapy and ablative procedures, may be associated in an attempt to prolong survival or to palliate symptoms (e.g. pain).

Radioembolization, also known as Selective Internal Radiation Therapy (SIRT), is a form of intra-arterial brachytherapy used to treat primary liver cancer and liver metastases. Radioembolization uses glass (TheraSphere® produced by MDS Nordion Inc.) or resin (SIR-Spheres® produced by Sirtex Medical Inc.) microspheres including β-emitter 90Y. The potential benefits of radioembolization technology for CRC liver metastases treatment can be significant in terms of economical and organizational impact and important ethical implications such as patient's expectations and hopes.

Objectives

Objectives of this HTA report were: i) to assess the clinical effectiveness of SIRT; ii) to analyse the clinical use of SIRT in Italy; iii) to carry out a cost and organizational analysis on the use of SIRT iv) to collect information on patients expectations and quality of life with SIRT.

Methods

For clinical effectiveness analysis we carried out a systematic review of literature, including studies on people aged 18-80 with non-resectable liver metastases from primary CRC. The Intervention assessed was SIRT using Yttrium^{90} coated microspheres administered via the hepatic artery compared to chemotherapy at 2nd and later lines and excluding supportive therapy.

We carried out a literature search on the following databases: MEDLINE, EMBASE, Cochrane Library, Health Technology Assessment websites, trial registries. We aimed to include HTA reports, systematic reviews and comparative prospective primary studies (trials and cohort studies) carried out from 1997 to date in English or Italian.

Data on study design, study population, SIRT and comparator outcomes were extracted. We assessed studies according to randomization, generation of the allocation sequence, allocation concealment, blinding and follow up. Interpretation of the studies' results was carried out in terms of numerousness, quality and consistency.

We performed a context analysis of the nineteen Italian Centres which were probably performing SIRT for the treatment of liver metastases from CRC. We adopted a questionnaire to collect data and information on diffusion, type of technology and resources used, data on clinical outcomes patient selection and costs of procedure.

We conducted a systematic review of the Italian and international scientific literature to identify and describe the economic evaluation studies of SIRT for liver metastases from primary CRC. We carried out a cost analysis of SIRT technology using data collected from questionnaires.

Finally, we used different sources of information to collect views and hopes of patients who used SIRT. First via Google search engine we identified websites, blogs and forums reporting narratives from patients with liver metastasis due to CRC who had or were going to have radioembolization. We then focused on primary studies which measured Quality of life with SIRT and collected some expert opinions.

Results

Systematic review

We identified and extracted one small open label randomized trial carried out on 46 patients. The trial appeared to show a benefit in terms of shortening time to liver progression (TTLP) and time to progression (TTP) of the disease of around 3 months. The study is small and judgment on the generalizability of its results to the Italian setting is unclear in the light of the results of our national survey. No other studies fitting our inclusion criteria were identified.

Context Analysis

All responders performing SIRT are equipped with the appropriate technology such as CT, Angiography, PET-CT and SPECT and with all key professional figures required.

Up to now SIRT in Italy was used as 1st-line in only about one fifth of all patients treated (21.2%), echoing the general opinion that chemotherapy still represents the best option as 1st-line treatment. The majority of hospitals (54.5%) preferred to provide SIRT in one session, while only two hospitals in two sessions and the remaining three of them in one or two sessions. Choice of number of sessions depended on not only cost but most importantly extension of metastatic

disease (unilobar, bilobar), reduction of technical complications potentially related to several sessions, different vascular supply of liver metastases and different response of each metastatic nodule to chemotherapy.

Fifty percent of liver involvement is the highest acceptable threshold in all hospitals. On this basis the number of liver metastases doesn't seem to be a selection criterion. Overall, the current patient selection threshold is higher than the past. This is to guarantee the lowest risk of toxicity, the highest chances of response, the best quality of life and also cost containment. Centres chose how to employ SIRT essentially in function of ongoing protocols at their respective sites: however, in comparison with use of SIRT a few years ago, an increasing number of Centres are employing it in early therapeutic lines (2nd, 3rd). The increasing rates of responses observed in different subsets of patients allowed testing SIRT in patients who had received i.v. chemotherapy.

Emerging SIRT Centres initially selected patients in more advanced lines of treatment, even for testing feasibility and safety at each respective clinical site. Considering the therapeutic potential of SIRT, in Italy the impact of SIRT should be tested with a larger use of prospective studies, similarly to clinical strategies promoted by other countries. Moreover our survey shows that the number of patient yearly treaded is relatively small with no more than 12 patients treated per year. Consequently a national resource optimization plan is needed.

Cost Analysis

The only study included in the effectiveness review did not have sufficient data on the effects for a cost-effectiveness analysis, as the results in terms of survival rate were not robust. Unfortunately, data on QALYs were also not available. For this reason only a cost analysis and a (partial) BIA were performed considering the real context data. During 2012 the number of patients that received SIRT was 25 (and 35 procedures).

Data from the survey instead are not enough reliable to determine how many patients with liver metastases from CRC actually perform the diagnostic work up resulting not eligible for SIRT treatment.

Literature searches did not provide information on this percentage, so we don't know how many additional costs should be considered in the budget analysis.We calculated the total cost of the SIRT procedure adding the costs of diagnostic work-up, treatment and follow up. The median cost is 15,229 Euros ranging from 13,582 to 17,370 Euros. The costs of an individual dose of radioisotopes amount to 10,000 euro. Total cost of the SIRT treatment in 2012 is 533,015 Euros (35 procedures).The total cost considering the minimum and maximum costs ranges from 393,878 to 503,730 Euros.

Patients views

For patients being able to undergo radioembolization means having a further chance of surviving cancer. Thus the attitude toward this treatment is usually positive and its probable side effects are regarded as tolerable. We found only one study, although not a RCT, which measured QoL with standardized questionnaires. Authors of the study concluded that patients QoL did not get worst with SIRT. Any future study comparing radioembolization with other therapies should always include QoL as a secondary outcome measured with standardized and internationally validated instruments.

Discussion

The results of our systematic review show that the combination of SIRT with chemotherapy vs. chemotherapy alone for the treatment of colorectal liver metastases may have a potential benefit in terms of shortened time to liver progression (TTLP) and time to disease progression (TTDP) of around 3 months.

However, these results come from the single trial identified in our systematic review with a limited number of participants.

The results of our survey of harms of SIRT show that pain and fever are the most common adverse experiences reported. However, these events could be also be interpreted as a good response to the treatment because they may be induced by tumour necrosis.

Our survey shows a scatter of many different Italian Hospital Centers performing SIRT on a small number of cases. In some cases these may have been part of study protocols for formal scientific investigations. This may explain the irregular pattern of provision of the therapy. A more rational use of resources would involve concentration of all patients in a smaller number of qualified Hospitals doing higher volumes of SIRT and accruing experience with the technique.

The potential costs of SIRT should require an exhaustive and complete economic evaluation in terms of cost per outcome (survival and QALY) compared with standard interventions to guarantee the best evidence base for decision-making.

Data from our context analysis showed a complexity of organization and management aspects due to the variety in professionals, skills, and equipment involved. Costs estimates from our survey reflect this complexity. The total costs per procedure estimated in this report (Euros 15,229) are higher than those reimbursed (using different codes) to hospital.

The finding that 10 years after the approval of the technique for such a late and intractable form of cancer, evidence of its effects is thin and its effects on quality of life are almost unknown.

Given the potential large costs of the intervention and the apparently promising nature of its effects on life, its quality and its acceptability to vulnerable patients, robust evidence is required.

Recommendations

Evidence on the effectiveness of the use of SIRT for the treatment of liver metastases from colorectal carcinoma is very limited, although several multi-center studies are in progress.

We recommend that the results of completed and nearly completed trials currently still active, be reported at the earliest opportunity. Ideally this could be done directly as preliminary summary results on the clinicaltrials.gov website.

Given the nature and stage of the disease in which patients are candidates for treatment, the cost of the SIRT and the uncertainty surrounding its effects, the adoption of the SIRT treatment would be advisable in few selected cases to concentrate in few qualified high specialized centres.

Sintesi

Introduzione

Il tumore del colon retto (CRC) è uno dei più frequenti nel mondo occidentale, con una prevalenza di 300.000 casi in Italia. Nel corso del 2012 sono attesi 52.000 nuovi casi. Le metastasi epatiche da CRC si sviluppano nel 50% dei pazienti ma sono resecabili solo nel 25%. Il tasso di sopravvivenza a cinque anni dopo l'intervento chirurgico è compreso tra il 20% e il 40%.

L'obiettivo principale del trattamento delle metastasi epatiche da colon consiste nel ridurre la dimensione e la diffusione delle lesioni. La resezione chirurgica rimane il trattamento di elezione a cui può ricorrere solo dal 10 al 25 per cento dei pazienti a causa di vincoli anatomici, riserva funzionale epatica inadeguata, o comorbilità concomitanti quali l'insufficienza cardiaca. Per la forma tumorale metastatica non resecabile, il trattamento di elezione è la terapia medica sistemica (chemioterapia) a cui possono essere associate terapie locali, come la radioterapia loco-regionale e le procedure ablative, nel tentativo di prolungare la sopravvivenza o per attenuare i sintomi (es. dolore).

La radioembolizzazione, conosciuta anche come Selective Internal Radiation Therapy (SIRT), è una forma di brachiterapia usata per il trattamento dell'epatocarcinoma e le metastasi epatiche. La SIRT utilizza microsfere di vetro (TheraSphere® prodotto da MDS Nordion Inc.) o resina (SIR-Spheres® prodotto da Sirtex Medical Inc.) e contengono 90Y che è un β-emettitore. I potenziali vantaggi della tecnologia di radioembolizzazione per il trattamento delle metastasi al fegato da CRC possono essere significativi in termini di impatto economico ed organizzativo oltre etico alimentando aspettative e speranze nel paziente.

Obiettivi

Gli obiettivi sono di: i) valutare l'efficacia clinica della SIRT; ii) studiare le modalità di utilizzo clinico della SIRT in Italia; iii) effettuare un'analisi dei costi e degli aspetti organizzativi; iv) raccogliere le informazioni sull'aspettativa dei pazienti e la loro qualità di vita.

Metodi

Al fine di valutare l'efficacia clinica è stata effettuata una revisione sistematica della letteratura, che include pazienti di età compresa tra 18-80 anni con metastasi epatiche da CRC non resecabili. Si sono presi in considerazione gli studi comparativi in cui si confrontano gli effetti della SIRT con microsfere di Ittrio-90 somministrate attraverso l'arteria epatica in pazienti dalla 2ª linea in poi

rispetto al trattamento con sola chemioterapia, escludendo il trattamento a scopo compassionevole.

La ricerca bibliografica è stata effettuata utilizzando i seguenti database: MEDLINE, EMBASE, Cochrane Library e siti web di Health Technology Assessment e Clinical trial. Il criterio di selezione degli studi si è esteso a tutti i report HTA, revisioni sistematiche e studi primari comparativi (trial e di coorte) pubblicati dal 1997 ad oggi in italiano o in inglese.

Da questi studi si sono estratte informazioni riguardanti il disegno, la popolazione, gli outcome della SIRT e del comparatore. Gli stessi sono stati valutati analizzando i criteri di randomizzazione, la sequenza di assegnazione, l'occultamento della lista, la cecità e il follow-up. L'interpretazione dei risultati degli studi è stata effettuata in termini della loro numerosità, qualità e consistenza.

Abbiamo effettuato un'analisi di contesto sui diciannove centri italiani che utilizzano la SIRT e che potenzialmente potrebbero utilizzarla per il trattamento delle metastasi epatiche da CRC. Si è utilizzato un apposito questionario al fine di raccogliere dati e informazioni circa la diffusione, il tipo di tecnologia e di risorse utilizzate, i dati sugli esiti clinici selezione dei pazienti e i costi della procedura.

Abbiamo condotto una revisione sistematica della letteratura scientifica italiana e internazionale per identificare e descrivere gli studi di valutazione economica della SIRT per il trattamento delle metastasi epatiche da CRC ed effettuato un'analisi dei costi della SIRT utilizzando i dati raccolti dai questionari.

Infine, abbiamo utilizzato diverse fonti di informazione per raccogliere le opinioni e le aspettative dei pazienti che hanno utilizzato la SIRT. Dapprima, tramite il motore di ricerca Google, individuando e raccogliendo sui siti web, blog e forum, le narrazioni dei pazienti che avevano ottenuto o che sono in procinto di ricevere il trattamento. Successivamente ci siamo concentrati sugli studi primari che hanno misurato la qualità della vita con la SIRT e raccolto alcuni pareri di esperti.

Risultati

Revisione sistematica

Abbiamo individuato ed estratto solo uno studio randomizzato effettuato su 46 pazienti. Il trial sembra mostrare un beneficio in termini di riduzione del tempo di circa 3 mesi della progressione epatica (TTLP) e del tempo alla progressione della malattia (TTP). Lo studio non è esteso e il giudizio sulla generalizzabilità dei suoi risultati nel contesto italiano non è così chiaro alla luce anche dei risultati rilevati dalla survey condotta. Non sono stati individuati altri studi che corrispondono ai nostri criteri di inclusione.

Analisi di contesto

Tutti i centri che effettuano la SIRT dispongono di tecnologie appropriate, come TAC, angiografo, PET-TC e SPECT e di tutte le figure professionali necessarie.

Ad oggi, in Italia, la SIRT viene utilizzata in 1ª linea solo su un quinto di tutti i pazienti trattati (21,2%), e pertanto, in questa linea, la chemioterapia rappresenta ancora l'opzione migliore. La maggior parte degli ospedali (54,5%) preferisce somministrare il trattamento SIRT in un'unica sessione, solo due centri in due e i restanti tre in una o due sedute. La scelta del numero di sedute dipende non solo dal costo, ma soprattutto dall'estensione delle metastasi (uni-lobare, bi-lobare), dalla riduzione delle complicazioni potenzialmente correlate alla somministrazione in diverse sessioni, dalla diversa vascolarizzazione delle metastasi epatiche e dalla diversa risposta di ogni nodulo metastatico alla chemioterapia.

Il cinquanta per cento del coinvolgimento epatico è la soglia più alta di accettabilità utilizzata in tutti i centri. Sulla base di questo parametro il numero di metastasi epatiche non sembra essere un criterio di selezione. Complessivamente, l'attuale soglia di selezione del paziente è superiore al passato. Questo al fine di garantire un più basso rischio di tossicità, le più alte probabilità di risposta, la migliore qualità di vita e anche il contenimento dei costi. I centri utilizzano la SIRT essenzialmente in funzione dei protocolli in uso nelle singole strutture: tuttavia, rispetto a qualche anno fa, un numero crescente di centri stanno impiegando l'utilizzo della SIRT in linee terapeutiche sempre più precoci (2ª, 3ª). L'aumento del tasso di risposta osservato nei diversi sottogruppi di pazienti ha consentito di testare la SIRT nei pazienti che avevano ricevuto la chemioterapia per via intravenosa.

Inizialmente i centri selezionavano i pazienti in linee più avanzate di trattamento, anche per testare la fattibilità e di sicurezza della metodica nel proprio contesto. Considerando il potenziale terapeutico della SIRT, il suo impatto dovrebbe essere testato attraverso un uso più diffuso di studi prospettici, così come accade in altri paesi. Inoltre la nostra indagine mostra che il numero di pazienti trattati ogni anno è relativamente esigua, non più di 12 pazienti. Di conseguenza, si rende necessario un piano nazionale di ottimizzazione delle risorse.

Analisi dei costi

L'unico studio incluso nella revisione dell'efficacia non disponeva di dati utili alla conduzione dell'analisi di costo-efficacia poiché i risultati in termini di sopravvivenza non erano robusti. Sfortunatamente non sono disponibile neppure dati sui QALY. Per questi motivi è stata eseguita solo un'analisi dei costi e una (parziale) BIA utilizzando i dati reali provenienti dall'analisi di contesto. Il numero di pazienti che hanno ricevuto il trattamento SIRT nel 2012 è pari a 25 (equivalenti a 35 procedure). Le informazioni ricavate dalla survey invece non sono stati sufficientemente affidabili per determinare quanti pazienti con metastasi epatiche da CRC

attualmente eseguono il work up diagnostico ma non la SIRT e in letteratura questo dato non è fornito. Quindi non è stato possibile calcolare il totale dei costi aggiuntivi da imputare nella BIA. Abbiamo calcolato il costo totale della procedura SIRT aggiungendo i costi di work-up diagnostico, trattamento e follow up. Il costo medio è di €15.229,00 che va da un minimo di €13.582,00 ad un massimo di €17.370,00. I costi di una singola dose è pari a 10.000,00 euro. Il costo totale del trattamento SIRT nel 2012 è stato di 533.015,00 euro (35 procedure). Il costo totale, considerando i costi minimi e massimi, varia da 393.878 a 503.730 euro.

Il punto di vista dei pazienti

Per la tipologia di pazienti da noi considerata sottoporsi alla radioembolizzazione significa avere un'ulteriore possibilità di sopravvivenza. L'atteggiamento verso questo tipo di trattamento è dunque, di solito, positivo mentre i suoi probabili effetti collaterali sono considerati tollerabili. Abbiamo reperito un solo studio (non randomizzato e controllato) in cui si sia misurata, con questionari standardizzati, la Qualità della Vita dei pazienti sottoposti a radioemblizzazione per metastasi al fegato dovute a CRC. Gli autori dello studio evidenziano come i pazienti trattati con SIRT non abbiano avuto un peggioramento della propria qualità di vita. In futuro, tutti gli studi che confronteranno la radioembolizzazione con altre terapie dovranno sempre includere la QoL come outcome secondario, misurandolo con strumenti standardizzati e validati a livello internazionale.

Discussione

I risultati della nostra revisione sistematica mostrano che, per il trattamento delle metastasi epatiche da tumore del colon retto, la combinazione di SIRT con il trattamento chemioterapico rispetto alla sola chemioterapia può avere un potenziale beneficio in termini di riduzione del tempo alla progressione epatica (TTLP) e del tempo di progressione alla malattia (TTDP) di circa 3 mesi.

Tuttavia questi risultati provengono da un solo studio, selezionato dalla nostra revisione sistematica che ha come limite di basarsi su una esigua serie di casi.

I risultati della nostra survey circa gli effetti collaterali mostrano che il dolore e la febbre sono gli eventi più comunemente riportati. Tali eventi, però, potrebbero essere interpretati come segnale positivo di risposta al trattamento derivante dall'effetto indotto dalla necrosi tumorale.

La nostra survey mostra che in Italia il trattamento SIRT viene offerto in molti centri ospedalieri, ciascuno dei quali tratta un numero limitato di pazienti. Inoltre l'adesione di questi centri a protocolli di studio potrebbe spiegare la diversità dei piani terapeutici somministrati.

Un uso più razionale delle risorse suggerirebbe la concentrazione di tutti i pazienti in un numero minore di ospedali, ben qualificati, di provata esperienza e considerati di riferimento per questa patologia.

L'assenza di studi economici nella nostra revisione può in parte derivare dalla mancanza di prove di efficacia della SIRT.

Al fine di supportare il processo decisionale una valutazione economica esaustiva e completa dovrebbe mettere in relazione i costi con gli outcome (sopravvivenza e QALY) del trattamento SIRT preso in esame rispetto a quello standard utilizzato nella pratica clinica.

Le informazioni rivenienti dalla survey evidenziano la complessità organizzativa in relazione alle numerose figure medico specialistiche coinvolte, alle competenze e alla dotazione tecnologica.

Anche la stima dei costi rilevati nella nostra survey riflette questa complessità. I costi totali stimati per ciascuna procedura (Euro 15,229) sono superiori a quelli rimborsabili (utilizzando codici diversi) con l'attuale sistema di remunerazione dei ricoveri.

Considerato che la tecnologia è in commercio da ormai 10 anni le prove di efficacia per il trattamento di forme di tumori avanzati e intrattabili sono poco robuste e sono quasi inesistenti i suoi effetti sulla qualità della vita.

Considerato gli elevati costi, la natura apparentemente promettente dei suoi effetti e la sua accettabilità da parte dei pazienti, una evidenza scientifica robusta è palesemente in ritardo.

Raccomandazioni

Le prove di efficacia dell'utilizzo della SIRT per il trattamento delle metastasi epatiche da carcinoma del colon-retto sono molto limitate, sebbene diversi studi multicentrici siano in corso di svolgimento. Si consiglia di segnalare tempestivamente i risultati rinvenienti dagli studi appena conclusi e di quelli ancora attivi in via di completamento, pubblicando ad esempio i risultati preliminari sul sito web clinicaltrials.gov.

Considerata la natura e lo stadio della malattia, come anche i notevoli costi e l'incertezza circa l'efficacia della SIRT, i risultati risultano essere di difficile interpretazione.

Considerata la natura e lo stadio della malattia in cui si trovano i pazienti candidati al trattamento, i costi della SIRT e l'incertezza che circonda i suoi effetti, l'adozione del trattamento SIRT sarebbe consigliabile in pochissimi e selezionati casi da concentrarsi in centri qualificati di alta specializzazione.

1. Background

1.1 Selective Internal Radiation Therapy (SIRT) in colorectal liver metastases: indication and clinical problems

The primary aim of treating colorectal cancer (CRC) liver metastases is to improve survival with an acceptable quality of life. Secondary objectives are to decrease the lesions' size and spread. Surgical resection is the treatment of choice in resectable colorectal metastases. However, only 10 to 25 percent of patients with isolated liver metastases are eligible for resection because of anatomical constraints (tumor location or extent of metastatic lesions), inadequate hepatic functional reserve, or concurrent medical co-morbidities such as poor performance status and cardiac failure [Burak 2011]. For unresectable metastatic disease, systemic medical therapy (chemotherapy) is the first choice treatment, but local therapy such as loco-regional radiotherapy and ablative procedures, may be associated in an attempt to prolong survival or to palliate symptoms (e.g. pain) [ISS 2012].

Radioembolization, also known as Selective Internal Radiation Therapy (SIRT), is a form of intra-arterial brachytherapy used to treat primary liver cancer and liver metastases. Radioembolization uses glass or resin microspheres including β-emitter ^{90}Y. The potential benefits of radioembolization technology for CRC liver metastases treatment can be significant in terms of economical and organizational impact and important ethical implications such as patient's expectations and hopes.

1.2 Epidemiological data and population

CRC is one of the most frequent cancers in the western world, with a prevalence of 300,000 cases in Italy. During 2012, 52,000 new diagnoses were expected in Italy, representing almost 14 percent of all cancer diagnoses [AIOM, AIRTUM 2012]. Patients with metastatic disease at diagnosis (stage IV) represent about 30% of new CRC diagnoses [ISS 2012]. Liver metastases from CRC develop in 50% of patients but only a proportion of those are considered to have resectable metastases [Leonard 2005]. The five-year survival rate after surgery is twenty to forty percent [AIOM, AIRTUM 2012].

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2. Description of SIRT

2.1 The technology

As the incidence of primary and metastatic liver cancer continues to increase [www.registri-tumori.it] the use of minimally invasive techniques as a treatment option is becoming more common. These new technologies include radiofrequency ablation, cryoablation, percutaneous ethanol ablation, chemoembolization (TACE) and radioembolization. The treatment of hepatic metastases depends on their extent and location.

Radioembolization uses microspheres (particles) made of glass or resin, impregnated with isotope Yttrium-90 (90 Y) beta emitter, which are infused through a catheter directly into the hepatic arteries [Lewandowski et al. 2007]. Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days).

The radioembolization technique is based on the fact that intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery and newly formed arterial vessels inside the cancerous tissue. The microspheres are injected selectively into the appropriate hepatic artery and subsequently become lodged in the microvasculature surrounding the tumor. Very high irradiation doses are delivered to the tumor, whereas the surrounding liver parenchyma is less affected by the radiation [Vente et al. 2009].

This HTA report focuses on devices commercially available in Italy and registered in the General Repertory of Medical Devices (RDM).

We searched the RDM (on 14th May 2013) using the National Classification of Medical Devices (CND) code ("CND Z11010380 - STRUMENTAZIONE PER BRACHITERAPIA RADIANTE - MATERIALI SPECIFICI" and "CND J99 – DISPOSITIVI IMPIANTABILI ATTIVI – ALTRI") and consulted manufacturers' websites. Two technologies were identified: TheraSphere® by MDS Nordion (Repertorio dei Dispositivi Medici, RDM, code is 145685/R) and SIR-Spheres® by Sirtex (Repertorio dei Dispositivi Medici, RDM, code is 267237/R) (Table 2.1).

Table 2.1: Devices for Selective Internal Radiation Therapy **(**SIRT) commercially available in Italy, registered within the General Repertory of Medical Devices (RDM).

Manufacturer	Device name	RDM	CE mark	FDA approval
MDS NORDION	TheraSphere®	145685/R	2005	1999 (Only in patient with unresectable hepatocellular carcinoma (HCC))
Sirtex	SIR-Spheres®	267237/R	2002	2002 (PMA)

Source: Data from RDM and free internet searches performed by Agenas.

2.2 Description of TheraSphere®

TheraSphere® by MDS Nordion Inc. obtained the CE mark in 2005 and obtained a Humanitarian Device Exemption (HDE) for TheraSphere by the FDA on Dec 10, 1999 (H980006).

TheraSphere® is used in the treatment of hepatic neoplasia, and consists of insoluble glass microspheres where Yttrium-90 is an integrated constituent of the glass. The glass radioactive microspheres (a mean diameter of 20-30 micrometers) are delivered directly to the liver tumours. TheraSphere® is available in 6 dose sizes: 3 GBq (81mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi) and 20 GBq (540 mCi). This device has a 12-day shelf life. Between 2 and 4 million microspheres are usually administered per treatment. TheraSphere® is a minimally embolic radioembolization device with a specific activity of 2,500 Bq per microsphere at the time of calibration. This relatively low embolic load allows infusion to proceed without concern for vascular stasis [Lewandowski R et. al, 2009].

2.3 Description of SIR-Spheres®

SIR-Spheres® by Sirtex Medical Ltd obtained the CE mark in 2002 for the treatment of liver tumours, and received FDA premarket approval application (PMA) for the treatment of hepatic metastases secondary to CRC in 2002.

SIR-Spheres® consists of millions of resin microspheres with an average diameter of about 32 microns (range 20 to 60 microns) loaded with yttrium-90. Typically about 13-40 million SIR-Spheres® microspheres (1.0 –1.5 GBq) are delivered in a treatment [Lewandowski R et. al, 2009]. The microspheres are suspended in sterile water so that they can be delivered by injection [Kennedy AS, 2006]. The SIR-Spheres® is a moderately embolic brachytherapy device with a specific activity of 50 Bq per microsphere at the time of calibration. This device has a 24-hour shelf life.

Comparison of Available Microspheres		
Parameter	**TheraSphere®**	**SIR-Spheres®**
Manufacturer	MDS Nordion Inc., Canada	Sirtex Medical Ltd, Australia
Material	Glass	Resin
Radionuclide	^{90}Y	^{90}Y
Size of particle	25 µm	35 µm
Vials available (GBq)	3-20	3
No. of spheres per 3-GBq Vial	1.2 million	40-80 million
Embolization	Low	moderate

Extract by (Lewandowski R et. al, 2009; Vente, 2009)

As discussed by Lewandowski R et. al. 2009, due the substantial differences between the two available devices, the ideal device should combine the desired radioactive and embolic effect to standardize treatment, infusion technique and administered dose.

2.4 Procedure

A patient being considered for SIRT will be admitted for a workup procedure before the treatment. As described in literature [Lewandowski et al. 2007] and confirmed by our clinicians and by the producers (MDS Nordion Inc. and Sirtex Medical Ltd) the pre-treatment workup consists of the following steps:

1. Angiography:

   - identify the hepatic vasculature feeding the tumour(s) to ensure that the blood supply to the tumour(s) is suitable for highly selective injection;
   - identify hepatic vascular connections to the Gastro Intestinal (GI) tract to ensure that these are sufficiently small to avoid radiation pneumonitis or radiation gastritis.

2. Injection of macroaggregated albumin labelled with Technetium-99m (99mTc-MAA):

this correlates closely with, and therefore predicts, the distribution of microspheres. Since there are limits to the exposure of lungs to shunted microspheres, a 99mTc-MAA study demonstrates the degree of hepato-pulmonary shunting and the connections between liver vascolarization and gastro intestinal tract that could result in delivery of radiation to non-target tissue [Leung T, 1995].

3. Single Photon Emission Computed Tomography (SPECT) scan using a gamma camera:

   - demonstrate the degree of lung shunting;
   - confirm avoidance of GI tract shunting;
   - map the deposition of MAA in target lesions and confirm the degree to which healthy tissue will be spared by radiation.

4. Review of SPECT scan:

   - calculate the lung shunt and confirm that it is below the acceptable threshold;
   - determine if SIRT is the appropriate treatment option;
   - establish the appropriate dose for the patient.

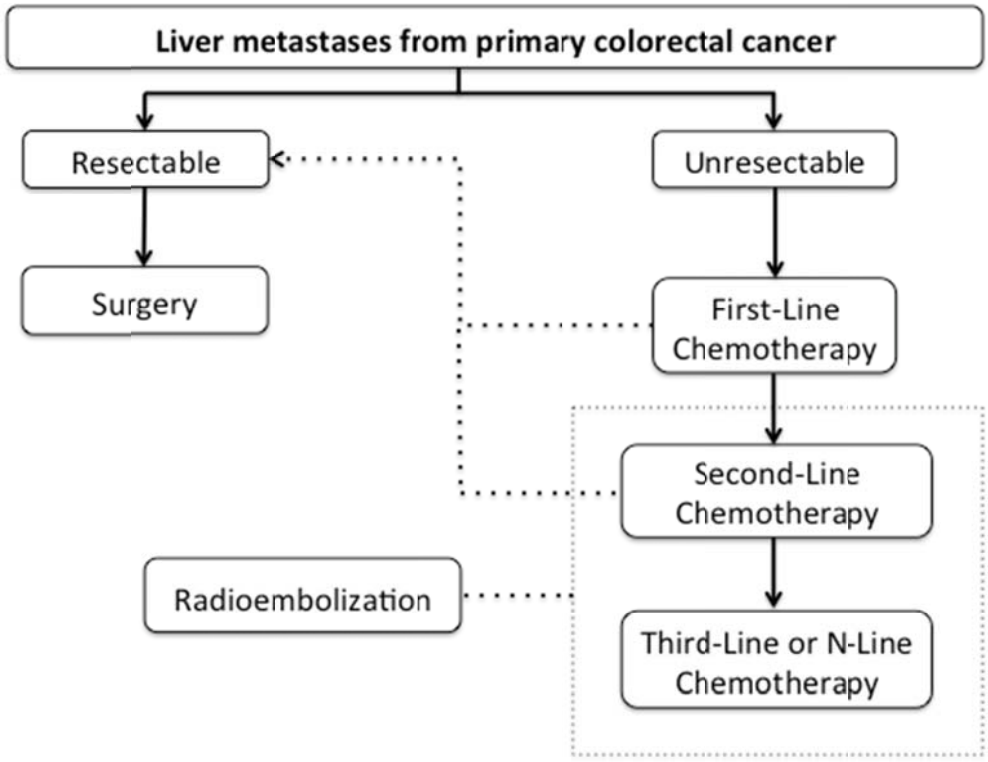
If SIRT is confirmed as the appropriate treatment option, the dose is ordered for a specified treatment date. This allows precise calibration of delivered radioactivity dose.
Under local anesthesia patients are injected with radioactive microspheres, that are designed to embolise into small vessels around the metastases, usually via a transfemoral catheter or a permanently implanted port with a catheter into the branches of the hepatic artery. For the

placement of this access port, patients may need to undergo laparotomy [NHS 2011]. SIRT can be administred in one or more sessons as described in context analysis (Chapter 5) according to the individual condition and protocol adopted.

The target areas can be defined using Technetium-99m micro aggregated albumin (^{99m}Tc MAA) planar nuclear scans, CT or ^{99m}Tc MAA SPECT. Angiographic mapping of the hepatic vascular tree can define the liver and tumor partitions further before radioembolization, including the extra hepatic connections and tumor vessels [Wan-Yee Lau et al. 2012]. Most of the preliminary examas as CT, ^{99m}Tc MAA Spect and angiography are performed in outpatient setting.

2.5 Alternatives

Patients with unresectable hepatic metastases from CRC are usually considered for systemic chemotherapy which is normally administered in an outpatient setting. In case of tumor progression the patient may be considered for a second-line chemotherapy or liver direct treatment, provided there are no extra hepatic metastases.



Source: Agenas

The current alternatives are: systemic chemotherapy including oxaliplatin or irinotecan combined with 5-FU, and sometimes a biological compound (Avastin®, Vectibix® or Erbitux®) or/and regional chemotherapy such as hepatic artery chemotherapy (HAC) [Rizell et al. 2010].

Radioembolization is used in selected patients with limited or no extra hepatic disease for the treatment of CRC liver metastases that are unsuitable for resection or ablation. It may be used

alone or in combination with chemotherapy. It aims to deliver radiation directly into the metastases, minimizing the risk of radiation damage to healthy surrounding tissues.

2.6 Characteristics of the hospital where SIRT can be performed

According to our clinicians and the documentation provided by producers, a Hospital Centre can perform SIRT in safety under the following conditions:

1. Presence of a tumor board to discuss patients with CRC liver metastases;
2. Presence of a nuclear Medicine Unit with license to store and dispose of Yttrium-90 and a hot lab to prepare the activity;
3. Presence of a planar gamma camera and/or SPECT-CT to perform the Technetium-99m labelled MAA scan after the pre-treatment work-up procedure and the Bremsstrahlung scan after SIRT administration;
4. Presence of interventional radiology suite, equipped with an angiography, also licensed to use Yttrium-90 within interventional procedures;
5. Presence of a license for authorized users to administer Yttrium-90 microspheres;
6. Presence of a medical Physics Unit with facility to perform Yttrium-90 dosimetric calculations and manage radiation protection before, during and after the procedure.

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3. Objectives, policy and research questions

To assess the impact of radioembolization therapy in adjunct to a standard chemotherapy of 2nd and later lines in patients with non-resectable liver metastases from primary colorectal adenocarcinoma.

Policy question

What is the impact on the Italian NHS of adding radioembolization with ^{90}Y-Microspheres to current treatments for patients with non-resectable liver metastases from primary CRC?

Research questions

What are the effects of adding radioembolization to 2nd and later lines of chemotherapy in patients aged 18-80 with non-resectable liver metastases from primary CRC in terms of: overall survival rates, response rate, time to progression, quality of life and patients' expectations, toxicity, cost per QALY, cost per treatment line.

4. Assessing the effectiveness from clinical studies

4.1 Systematic review

The systematic review (SR) aims to identify evidence of the effects (efficacy and effectiveness) of adding radioembolization to 2nd and later lines of chemotherapy in patients aged 18-80 with non-resectable liver metastases from CRC.

4.2 Objectives of the systematic review

The objective is to provide an overview of available evidence on the benefits of treating patients aged 18-80 with non-resectable liver metastases from primary CRC with SIRT in addition to 2nd line or later line chemotherapy.

4.3 Methods

Inclusion criteria

We aimed to include studies on people aged 18-80 with non-resectable liver metastases from primary CRC. Studies with more than 25% of over 80-years-old subjects were excluded. The Intervention assessed was selective internal radiation therapy using Yttrium-90 coated microspheres (glass or resin), administered via the hepatic artery compared to chemotherapy at 2nd and later lines and excluding supportive therapy.

We looked at the effects on survival rates: disease free survival, progression free survival, liver disease free survival, response rate, downstaging, time to progression, quality of life, toxicity and side effects.

We aimed to include HTA reports, systematic reviews and comparative prospective primary studies (trials and cohort studies) carried out from 1997 to date in English or Italian.

Literature search

We carried out a literature search on the following databases: MEDLINE, EMBASE, Cochrane Library, Health Technology Assessment websites, trial registries. The literature search strategy is described in Appendix 1.

Study selection

We used the ProCite software (version 5 for MS Windows) to manage retrieved studies. The selection of studies to be included was managed following these steps:

- exclusion on the basis of title and abstract;
- full text retrieving of potentially interesting studies;
- reading of selected articles and application of the inclusion criteria.

Data extraction

Data on study design, study population, SIRT and comparator outcomes were extracted. Data extraction from the included study was carried out using a single study table of evidence. Extraction was performed by two independent reviewers. The results of the extraction were compared and differences discussed. Resolution of the differences in the extraction was achieved by mutual agreement.

Methodological quality assessment

We screened potential articles for inclusion and extracted data on standardised sheets (see Appendix 2). Assessment of methodological quality for randomized controlled trials was carried out using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2011]. We assessed studies according to randomization, generation of the allocation sequence, allocation concealment, blinding and follow up.

We assessed quality of non-randomized studies in relation to the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS) [Wells 2012].

Analysis and synthesis

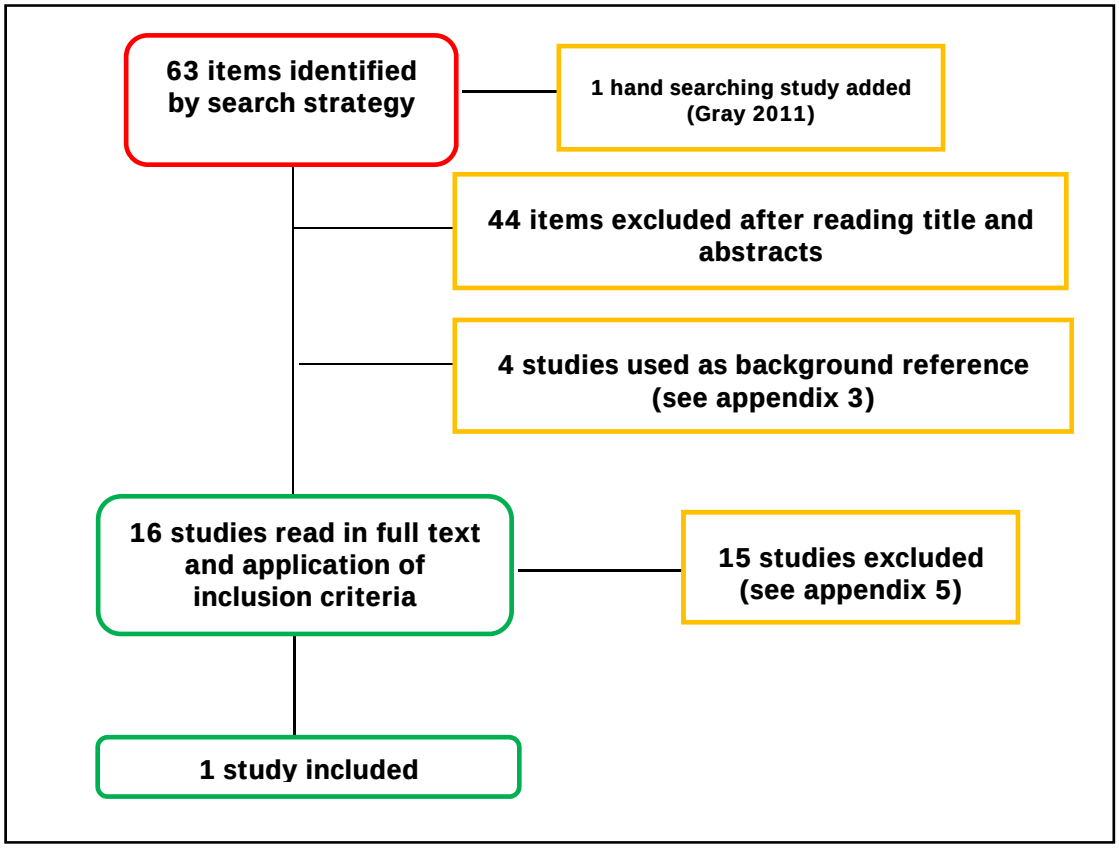
We used quality at the analysis stage as a means of interpreting the results. In observational studies we assigned risk of bias categories on the basis of the number of NOS items judged inadequate in each study: low risk of bias - up to one inadequate item, medium risk of bias - up to three inadequate items, high risk of bias - more than three inadequate items, very high risk of bias - when there was no description of methods.

Interpretation of results

Interpretation of the studies' results was carried out in terms of numerousness, quality and consistency.

4.4 Results of the systematic review

Figure 4.1 - Flow diagram of the studies



We identified and extracted one study reporting a small open label randomized trial carried out on 46 patients in Belgium (Hendlisz 2010) (Figure 4.1). The trial appeared to show a benefit in terms of shortening time to liver progression (TTLP) and time to progression (TTP) of the disease of around 3 months. No other studies fitting our inclusion criteria were identified. The list of background references is in Appendix 3; the included study is in Appendix 4. Appendix 5 reports the list of excluded studies.

The trial by Hendlisz et al is small and judgment on the generalizability of its results to the Italian setting is unclear in the light of the results of our national survey.

4.5 Clinical Trials registered in clinical trials.gov

We identified 6 trials comparing SIRT with different types of chemotherapy (Table 4.2).

Table 4.2. Registered clinical trials of SIRT/Radioembolisation for hepatic metastases of colorectal carcinoma (from clinicaltrials.gov. Accessed on 5 June 2013).

NCT Number	Title	Recruitment	Interventions	Sponsor/ Collaborators
NCT01721954	FOLFOX6m Plus SIR-Spheres Microspheres vs FOLFOX6m Alone in Patients With Liver Mets From Primary Colorectal Cancer	Recruiting	Drug: FOLFOX6m|Device: SIR-Spheres microspheres	Sirtex Medical
NCT01483027	Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer	Recruiting	Device: TheraSphere	Nordion (Canada) Inc.
NCT01186263	Predictive Value of 99mTc-Albumin Spheres Before 90Y- SIR Therapy	Recruiting	Drug: MAA for diagnostic SPECT imaging|Drug: Diagnostic B20- SPECT imaging.	University of Magdeburg|Sirtex Medical
NCT00766220	Yttrium Microspheres With Cetuximab Plus Irinotecan for Patients With Advanced Colorectal Cancer Mets to Liver	Withdrawn	Drug: SIR-spheres Agent Administration|Drug: Cetuximab|Drug: Irinotecan	M.D. Anderson Cancer Center|Sirtex Medical
NCT00724503	FOLFOX Plus SIR-SPHERES MICROSPHERES Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer	Active, not recruiting	Drug: Systemic chemotherapy (FOLFOX)|Device: SIR-Spheres yttrium-90 microspheres|Drug: Systemic chemotherapy (FOLFOX)	Sirtex Medical
NCT00199173	Comparing Hepatic Intra-arterial Injection of Yttrium-90 Microspheres Versus Fluorouracil (5FU) in Colorectal Cancer Metastatic to the Liver Only	Completed	Device: SIR Spheres intra-arterial hepatic	Jules Bordet Institute|University Hospital, Ghent

The results of the study NCT00199173 were not available on clinicaltrial.gov at the time of writing.

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Hendlisz A, Van den Eynde M, Peeters M et al. Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy. Journal of Clinical Oncology, vol. 28 number 23, August 10 2010.

5. Context analysis

5.1 Objectives of the context analysis

We aimed to describe the spread of SIRT, the type of technology used, the clinical condition of patients treated, the eligibility criteria adopted, the clinicians involved and information on organization and costs within the context of the Italian NHS. Consequently, we planned a questionnaire survey (see Appendix 6).

5.2 Methods for context analysis

We performed a context analysis of Italian centers using SIRT through a questionnaire (see Appendix 6) sent to all nineteen Hospital Centers known to be performing radioembolization (see Appendix 7) to collect data and information on:

- Diffusion of the radioembolization procedure (number of patients treated, number of procedures, line-therapy and patient condition);
- Type of technology used;
- Resource used to perform radioembolization and organization;
- Unit costs of resources to perform radioembolization;
- Data on clinical outcomes and patient selection.

Hospital Centers were identified combining the customer list provided by manucturers: Nordion (Canada) Inc. and Sirtex Medical Inc..

For each identified Center, the questionnaire was sent by ordinary mail to the Director and by e-mail to the care giver for SIRT treatment (oncologist, interventional radiologist or nuclear physicians). All invited Centers replied to our invitation.

The costs are discussed in the economic model in Chapter 6.

5.3 Results of context analysis

Diffusion of SIRT in Italy

We sent 19 questionnaires and received 10 answers. SIRT is performed in 19 Hospital Centers but only in 10 it is used for the treatment of CRC liver metastases (Table 4.3); most of them are public hospitals, except the two private NHS accredited Hospitals: the Istituto Europeo di Oncologia (IEO) in Milan and "IRCCS Ospedale Casa Sollievo della Sofferenza" in San Giovanni Rotondo (Foggia).

Table 4.3 – Responding hospitals performing SIRT for CRC liver metastases in Italy (2012).

Hospital Center	City
Santa Maria Goretti Hospital	Latina
Istituto Regina Elena – IFO	Roma
Istituto Nazionale Tumori di Napoli - IRCCS "Fondazione G. Pascale"	Napoli
Policlinico S. Orsola Malpighi	Bologna
Azienda Ospedaliero Universitaria di Udine	Udine
Ospedale Ca' Foncello Di Treviso	Treviso
Istituto Europeo di Oncologia (IEO)	Milano
Azienda Ospedaliera "San Gerardo"	Monza
Azienda Ospedaliero Universitaria – Stabilimento di Cisanello	Pisa
IRCCS Ospedale Casa Sollievo della Sofferenza	S.G. Rotondo (FG)

Type of technology used

All hospitals (Table 4.3) use SIR-Spheres® for the treatment of patients with CRC metastases.

Resources used to perform radioembolization and organization

According to the best practices and the characteristics of the Hospital reported in Chapter 2, all centers are equipped with all the necessary technology and personnel for the pre-treatment workup, treatment and follow-up of patients. All responders performing SIRT are equipped with the appropriate technology such as CT, Angiography, PET-CT and SPECT and with all key professionals involved as: interventional radiologist, nuclear physicians, oncologist, physicist, medical physicists.

Data on clinical outcomes and patient selection

The first five Italian hospitals listed in Table 4.3 (Latina, Rome, Naples, Bologna and Udine) are part of the cooperating Liver Tumors Working Group of the Italian Society of Locoregional Therapy in Oncology (SITILO). The hospitals were previously involved in the first Italian prospective cohort on SIRT for unresectable, CRC metastases [Cosimelli et al., 2010]. They treat almost three fourths of patients treated with SIRT (47 out of 61, 77%) and represent the most important referral centers for the number of patients treated from 2005 and their clinical experience on SIRT. At present all have joined a randomized clinical trial on i.v. chemotherapy with or without SIRT as 2nd-line in patients with unresectable CRC liver metastases progressing in the liver after 1st-line of i.v. chemotherapy. In our survey 3.1% of patients were aged 80 or more while males represented about two thirds of all the patients treated.

Table 4.4 – Patients with CRC liver metastases treated with SIRT.

Hospitals	Year	Second to fourth line treatment	Over fourth line treatment	Total mCRC patients treated with SIRT
		®SIR-Spheres	®SIR-Spheres	®SIR-Spheres
Santa Maria Goretti Hospital (Latina)	2012	12	10	22
Regina Elena (IFO) (Rome)	2012	3	3	6
Istituto Pascale (Naples)	2012	8		8
S. Orsola Malpighi Hospital (Bologna)	2012	1 (1 patient , 2 treatments)		1
A.O. Universitaria di Udine (Udine)	2007	10		10
Ca' Foncello Hospital (Treviso)		2		2
IEO (Milan)	2009	4	0	4
San Gerardo Hospital (Monza)	2010/2011	4		4
Cisanello Hospital (Pisa)		2	1	3
IRCCS Sollievo della Sofferenza (S.G. Rotondo-FG)	2012	1	0	1
Total		47	14	61

Up to now SIRT in Italy was used as 1st-line in only about one fifth of all patients treated (21.2%), echoing the general opinion that chemotherapy still represents the best option as 1st-line treatment (Table 4.4). Nevertheless, large international, randomized phase III clinical trials (SIRFLOX, FOXFIRE) are now analyzing SIRT effectiveness added to chemotherapy and twelve hundred patients will be available for long-term results at the end of 2014. There is a strong rationale supporting the combination i.v. chemotherapy – SIRT to both reduce liver progression and improve survival, disease-free interval and quality of life.

The majority of hospitals (54.5%) preferred to provide SIRT in one session, while only two hospitals in two sessions and the remaining three of them in one or two sessions (Table 4.5). Choice of number of sessions depended mainly on extension of metastatic disease (unilobar, bilobar), reduction of technical complications potentially related to several sessions, different vascular supply of liver metastases and different response of each metastatic nodule to chemotherapy.

Table 4.5 – Number of SIRT treatment sessions.

Hospitals	1	2	>2	Interval between sessions (in days)	Performing SIRT in the some session	
					Yes	No
Santa Maria Goretti Hospital (Latina)		x		35-45		x
Regina Elena (IFO) (Rome)	x				x	
Istituto Pascale (Naples)*	x	x		30		x
S. Orsola Malpighi Hospital (Bologna)		x		30		x
A.O. Universitaria di Udine (Udine)	x	x		30		x
Ca' Foncello Hospital (Treviso)	x					x
IEO (Milan)	x				x	
San Gerardo Hospital (Monza)	x					x
Cisanello Hospital (Pisa)	x	x		40		x
IRCCS Sollievo della Sofferenza (S.G. Rotondo-FG)	x				x	

*** 1 session unilobar treatment, 2 sessions in bilobar treatment**

Fifty percent of liver involvement is the highest acceptable threshold in all hospitals (Table 4.6). On these bases, number of liver metastases doesn't seem to be an affecting factor for selection criterion. The number of extrahepatic metastatic sites ranged from 0 to 5, considering that liver progression mainly affects indication for SIRT the combination of SIRT with chemotherapy regimens allows coverage of all the metastatic sites. In comparison to past practice, limiting the cut-off levels of bilirubin at 2.5 as maximum value as well as considering an extrahepatic leakage not higher than 20% allowed significant reduction of liver toxicity. The majority of vascular abnormalities as well as previous liver resection did not contraindicate SIRT, since both embolization of side vessels and satisfactory liver diffusion of spheres can be achieved.

Overall, the current patient selection threshold is higher than in the past. This is to guarantee the lowest risk of toxicity, the highest chances of response, the best quality of life and also cost containment.

Table 4.6 – Criteria for patient selection.

Hospitals	Liver involvement		N. of extrahepatic metastases	N. of hepatic metastases	Line of chemotherapy administered			Bilirubin					Vascular abnormalities	Previous hepatic resection (N.)	Extrahepatic leakage (%)
	Residual segments after resection (N.)	Value %			max	min	median	min	max	median	INR	Platelets			
Santa Maria Goretti Hospital (Latina)		40	4	(3-10)	5	2	3.4	0.7	2.0	1.27		60000	12%	8	7
Regina Elena (IFO) (Rome)		<50%	max 1 extrahepatic site stable	N.A	3	1		within the limits	2		within the limits	>100.000	evaluated only during angiography	not standardized	<20%
Istituto Pascale (Naples)	4	max < 50%	0	multiple	5	2	3	1	2.5		1.5	60000	present	2	10
S. Orsola Malpighi Hospital (Bologna)		< 50%	0	N.A radioembolization treats all metastasis including multiple and bilateral ones)	n.a.	2	n.a.		2		<= 1.5	> 50.000	All vascular abnormalities previously treated with embolizationare eligible for treatment	Patients with pre-existing liver resections and good residual liver function are elegible to treatment	Hepatopulmonary shunt max 20% e max 30 Gray for the lung
A.O. Universitaria di Udine (Udine)									1.9		<2	> 50.000			
OspedaleCa' Foncello (Treviso)		< 50%	0	it is not a criterion for inclusion		2			2				Controls with selective embolization		<20% to the lung o 30 Gy
IEO (Milan)		>50%	depends on the location	depends on the size, not more than6	2								>50%		0%
San Gerardo Hospital (Monza)		max 50%	no metastases	not dependent on the number but from replaced iver volume	4	2	3						Anatomical variant with right hepatic artery originating as the first branch of the superior mesenteric artery division	1	0
Cisanello Hospital (Pisa)	no one was resected		<5 lung<1cm	no limit	3	1	2	0,3	0,7	0,5	0,93-1,2	200-300	It is not a contraindication	0	0
IRCCS Sollievo della Sofferenza S.G. Rotondo-FG)		50%	0											0	<40%

Centers chose how to employ SIRT essentially in function of ongoing protocols at their respective sites: however, in comparison with use of SIRT a few years ago, an increasing number of Centers are employing it in early therapeutic lines (2^{nd}, 3^{rd}) as in Latina, Rome, Bologna, Udine (Table 4.7) which first started to treat patients with unresectable, heavily pretreated CRC liver metastases in 2005, obtaining unexpectedly promising results in a phase II prospective study [Cosimelli et al., 2010]. The increasing rates of responses observed in different subsets of patients allowed to test SIRT in patients who had received i.v. chemotherapy.

Emerging SIRT Centers initially selected patients in more advanced lines of treatment, even for testing feasibility and safety at each respective clinical site.

The average of activity delivered in each treatment session, as reported by responding centers, varied from a minimum of 0.74 to a maximum of 1.97 GBq (tab 4.8), taking into consideration that the dose is sometimes divided and administered to two patients, even if the SIR Spheres are CE marked for “single use only”.

Table 4.7 – SIRT plus chemoteraphy

Hospitals	Second line		Third line		Fourth line	
	Yes	No	Yes	No	Yes	No
Santa Maria Goretti Hospital (Latina)	x		x		x	
Regina Elena (IFO) (Rome)	x		x			x
Istituto Pascale (Naples)	always		likely		likely	
S. Orsola Malpighi Hospital (Bologna)		x	x		x	
A.O. Universitaria di Udine (Udine)			x			
Ospedale Ca’ Foncello (Treviso)		x		x		x
A.O. Ospedale Di Circolo F. Macchi (Varese)						
IEO (Milan)		x		x		x
San Gerardo Hospital (Monza)		x		x		x
Cisanello Hospital (Pisa)		x		x		x
IRCCS Sollievo della Sofferenza (S.G. Rotondo- FG)		x		x		x

Table 4.8 – Activity administered by Centers

Hospitals	Activity administered X session (GBq average)
1	0.74
2	1
3	1.4
4	1.5
5	1.5
6	1.6
7	1.7
8	1.65
9	1.97

At the present time in Italy there is a gap between two groups of Centers in terms of SIRT experience. Considering the therapeutic potential of SIRT, in Italy the impact of SIRT should be tested with a larger use of prospective studies, similarly to clinical strategies promoted by other countries. Moreover our survey shows that the number of patient yearly treated is relatively small with no more than 12 patients treated per year. Consequently a resource optimization plan is needed within a National coordination plan.

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6. Economic analysis

6.1 Objectives of the economic analysis

The objectives of the economic evaluation of SIRT are to analyze the costs and consequences of adding SIRT to chemotherapy in comparison to standard chemotherapy in the Italian context. We carried out a systematic review of economic evaluation studies and we carried out a cost analysis and Budget Impact Analysis (BIA) relative to adding SIRT to standard therapy.

6.2 Systematic review of economic evidence of SIRT

6.2.1 Methods

We conducted a systematic review of the Italian and international scientific literature to identify and describe the economic evaluation studies of selective internal radiation therapy for liver metastases from primary CRC .

Inclusion criteria

The inclusion criteria were: economic evaluations based on all types of economic analysis (CEA, CUA, CBA; CCA; CMA) comparing the use of radioembolization with standard chemotherapic treatment from 1997 to date. Language Italian and English.

Literature search

We carried out a search of the literature on the following databases: MEDLINE, EMBASE, Cochrane Library.

Study selection

We used ProCite programme (version 5 for MS Windows) to manage retrieved studies.

Data extraction

We intended using an extraction sheet for data from studies. We wanted to perform extraction in double by two independent reviewers. We intended comparing the results of the extraction and discussing the differences. Mutual agreement was the method planned to overcome differences in the extraction.

Methodological quality assessment

We intended assessing methodological quality of included economic evaluations using the checklist for economic evaluations of health programmes [Drummond 1996].

Analysis and synthesis

We intended analyzing and synthesizing studies using a tabulation built on the basis of the data extraction form.

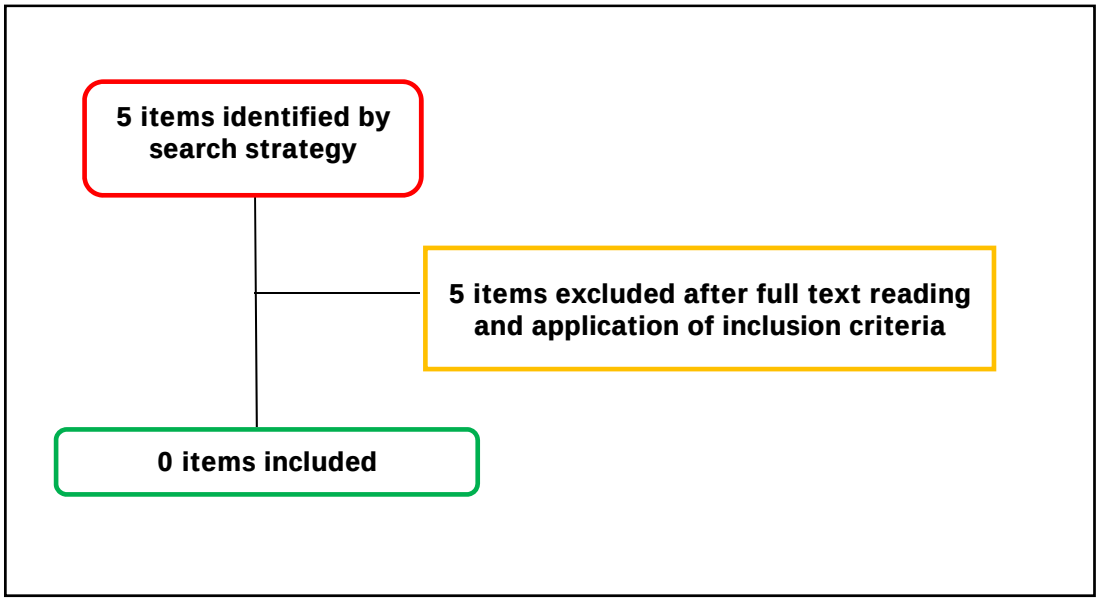
Interpretation of results

We aimed to interpret studies' results in terms of size, quality and consistency.

6.2.2 Results

The search strategy (reported in Appendix 8) identified 5 items for possible inclusion. We read all items in full text and no study on the cost effectiveness of SIRT in liver metastases from primary CRC fitted inclusion criteria and was therefore selected. A flow diagram of the studies is reported in figure 6.2. The List of excluded economic studies is reported in Appendix 9.

Figure 6.2 - Flow diagram of the studies



6.3 Cost analysis from the context analysis

This chapter aims to assess the economic aspect related to the use of SIRT. We performed an analysis on costs and resources used in the pathway of SIRT. We also carried out a BIA to calculate the total cost of treatment in 2012 in Italy based on current available data (see chapter 5).

6.3.1 Methods

We populated the cost evaluation with the cost-related information (staff time, cost of any tests associated to the technology; cost of equipment) reported by the context analysis. We carried out a BIA using data reported by the context analysis. We did not cost harms of either comparator.

6.3.2 Results

The survey conducted for the assessment of the context use (Chapter 5) of SIRT for mCRC had a section dedicated to the analysis of the resources and the costs related to the SIRT procedure. The cost section is always the most difficult to report for participating centers because the data were

not always easy to collect. This is our experience with this type of survey. Generally, while most of the responding centers stated the resources used and the time of each action or procedure ("Diagnostic Work up", "SIRT Treatment" and "Follow-up"), only 5 of the 10 responding centers calculated the total incurred costs.

"Diagnostic work up " - Resources and costs

Work up includes the diagnostic procedures to verify that clinical conditions of the patient were compatible with the SIRT treatment.The diagnostic work up was performed in an outpatient setting. In the questionnaire we asked to fill the code for the provision of specialist outpatient and relative fee (Regional or National). Table 6.8 shows the median values for each service item and the minimum and maximum fee applied by single centers. Detailed enumeration, measurement and valuation of each resource consumption item were not carried out.

Table 6.8. Median cost of work up procedures

Service item	Fee Median(€)	Fee Min (€)	Fee Max (€)
Liver study with ultrasound	47,52	43,9	79,75
CT for liver volume study	205,03	141	334
CEA	10,95	10,60	12,65
CA 19.9	16,57	16,40	17,00
PET-CT	1182,25	1071,65	1295,55
First hepatic and mesenteric artery arteriography	283,30	283,00	438,30
Scintigraphy with MMA	116,00	75,95	154,95

The diagnostic work up involves different clinical professionals. Almost all responding centers uses just one unit for each professional listed in Table 6.9 for a median time ranging from 30 to 60 minutes. However, the results within each professional category show a variability in the time range (e.g. varies from 5 to 180 for nuclear physician) probably due to difference in type of organization.

The presence of a psychological professional support is indicated as shown in the literature and also by one of the authors (M. Cosimelli). However, no center reported indications and data about the involvement of this professional figure. An interview with a psycho oncologist in Italy confirmed that hospitals (with the exception of one) that carry out SIRT are not expected to provide a specific psychological support (see also chapter 7 on patients' views).

Table 6.9. Professionals and time

	N.	Time (minutes)	TimeMin	TimeMax
Resources	**Median**			
Nuclear phisician	1	30	5	180
Oncologist	1	45	20	60
Interventional Radiologist	1	60	30	120
Medical Physicist	1	45	5	90
Nurse	1	60	30	180
Pathologist				
Psycho oncologist				
Radiology technician	1	60	45	120

Table 6.10 shows the median values and costs related to: angiography suite, biocompatible spirals used and hospital stay. Median hospital stay is two days (ranging from 1 to 3 days).

Table 6.10. Resources, time and costs.

	Time (median)/ N.	Range	Median Cost (€)
Angio suite	90	(40-120)	310
Biocompatible spiral	3	(1-6)	242
Hospital stay	2	(1-3)	350

"SIRT treatment procedure" - Resources and costs

Treatment procedure includes the injection of the radioisotopes. The injection is made during the execution of the hepatic arteriography during which also PET can be performed. However, outpatient specialist codes and relative fees for PET were not specified. Table 6.11 shows treatment procedure costs and median values whereas the professional resources are listed in Table 6.12. As in diagnostic work up, the median number of professionals involved is one, with a total median time ranging from 75 to 90. Furthermore we found a high variability in time within each professional category (e.g. from 20 to 180 minutes for nuclear physician). Finally in Table 6.13 we report the median time and cost of angiography suite and hospital stay.

Table 6.11. Treatment Cost.

	Cost (€) (Median)	Cost (€) Min	Cost (€) Max
Arteriography	283,00	75,95	438,30
Dose injection	**Dose COST € 10,000**		

Table 6.12. Professional time (expressed in minutes) involved in SIRT administration.

Skills	N	Time Median	Time Min	Time Max
Nuclear physician	1	75	20	180
Interventional Radiologist	1	60	40	90
Medical Physicist	1	60	15	120
Nurse	1	90	60	160
Psycho oncologist				
Radiology technician	1	90	60	90

Table 6.13. Other resource involved in SIRT treatment

	Time in minutes (median)	Range	Mediancost €
Angiography suite	75	(60 - 120)	3,30 (min)
Hospital stay	2 - days		350 (x day))

"Follow up" - Resources and costs

The objective of the clinical follow-up is to check the ability of the treatment to achieve the expected results in terms of effectiveness and benefits to patients. It is important for future planning of further treatment and procedures to be included in the clinical pathway of the patient. Patients who received SIRT are subjected to blood tests, CEA and TC to verify the change in the liver function and treatment's reaction. Median costs given by responding centers are shown in Table 6.14, whereas Table 6.15 shows a median time ranging from 15 to 30 minute for professional involvement.

Table 6.14. Follow up service items

Health services	Median Cost (€)	Range (€)
Blood tests*	9,00	(3-25)
CEA	10,85	(10,6-12,65)
CT	205,975	(141-314)
Specialist examination	20,8	(12,91-30)

* The variability is due to the number of blood tests performed

Table 6.15. Professional figures involved

	N.	Time (minutes)	Time Min	Time Max
Skills	**Median**			
Oncologist	1	30	20	60
Nuclear physician	1	30	20	60
Radiologist	1	30	30	120
Nurse	1	15	NR	NR
Psycho oncologist			NR	NR
Radiology technician	1	10	NR	NR
Radiologist physician	1	30	NR	NR

NR= Not Reported

The context analysis should have provided information about the chemotherapy drugs used in addition or in alternative to the SIRT treatment. Unfortunately, none of the responding centers provided data on drugs, so chemotherapy costs calculation was not possible.

6.4 Reimbursement of SIRT

It was difficult to assemble data about the reimbursement of SIRT taking into account that responding centers provided both single ICD-9-CM procedure codes that many codes to identify the whole procedure. Responding centers also provided either ICD diagnosis codes or procedure codes or DRG code for each step of the pathway (work up, treatment and follow up).

The majority of responding centers, furthermore, have no scheduled specific reimbursement for the follow up activities. Centers use different codes for reimbursement arrangements for work up, treatment and sometimes follow-up. In some case SIRT is reimbursed by dedicated financed projects (such as clinical investigations) or directly by patient (out of pocket). The difficulty of aligning the data does not allow us to synthesize and quantify, unless they are considered as individual cases.

6.5 Cost of the SIRT procedure

We calculated the total cost of the SIRT procedure adding the costs of diagnostic work-up, treatment and follow up. Table 6.16 shows the median cost and range of total cost for a single procedure. The median cost is 15,229 euro ranging from 13,582 to 17,370. The costs of an individual dose of radioisotopes amount to 10,000 euro.

Table 6.16. Cost for SIRT Treatment

Item	Cost median (€)	Cost min (€)	Cost max (€)
Diagnostic work up	1861,618	1642,5	2332,2
	1891	798,67	3122
Treatment	283	75,95	438,3
	10000	10000	10000
	947,5	898	1096
Follow up	246	167,51	381,65
Total	**15.229,118**	**13.582,63**	**17.370,15**

6.6 Budget Impact Analysis (BIA) of SIRT

The survey carried out among Italian centers that performed SIRT during 2012 shows that 29 patients were treated with SIRT for a total number of procedures of 35 (6 patients were retreated). Total cost of the SIRT treatments in 2012 were 533,015 Euro. However, it is possible that the dose is divided and administered to two patients, even if the SIR Spheres are CE marked for "single use only" as reported in the label.

In case of fractionation (as practised by some centers) the median total expenditure is around EUR 472,099. The total cost considering the minimum and maximum ranges from 393,878 to 503,730 Euros. The BIA, however, must take in account not only the costs for patients receiving SIRT, but also the costs for patients performing diagnostic work up who are subsequently found not to be candidates for treatment (for example because of the presence of a shunt). In this case, the BIA shall include also the percentage of costs incurred for the diagnostic work up. Data from the survey are not enough reliable to determine how many patients with liver metastases from CRC actually perform the diagnostic work up resulting not eligible for SIRT treatment.

Literature searches did not provide information on this percentage, so we don't know how many additional costs should be considered in the budget analysis. However, considering that the median cost of the diagnostic work up amounted to € 3,752 (range: 2441-5454), the budget impact could be estimated calculating this cost for the total number of patients enrolled for SIRT procedure even if patients do not receive treatment with SIRT.

6.7 Conclusion

Economic evaluation is a comparison of two or more alternatives involving technologies. In the HTA processes economic analysis represents a synthesis of other fields of evaluation (effectiveness and safety, context, organization). The dilemma of all health economists is to analyze the right steps and use the right technique of evaluation.

The only study included in the effectiveness review did not have sufficient data on the effects for a cost-effectiveness analysis, as the results in terms of survival rate were not robust. Unfortunately, data on QALYs were also not available. For this reason only a cost analysis and a (partial) BIA were performed considering the real context data.

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7. Patients views

7.1 Objectives

Our objectives were to find data on quality of life relative to radioembolisation in our target population and to obtain a better understanding of patient's perspectives, expectations and views on this therapy in relation to burden of disease, description of treatment and its side effects.

7.2 Methods

Individuals with metastatic liver cancer entering second line therapy are human subjects at a very vulnerable time in their lives. This raises ethical issues about their direct involvement in a qualitative research project aimed at collecting their views [Reid J. 2009; Im et. Al 2012, Flicker et al. 2004]. We decided to use the following sources of information on QoL in CRC patients with liver metastasis who used SIRT: spontaneous narratives from the internet, literature review and experts opinions from proxies with a specific expertise in treating this type of oncological patients.

We used the Google search engine to identify websites, blogs and forums that reported narratives from patients with liver metastasis due to CRC who had some hope of being eligible for radioembolization and have failed a first line chemotherapy. Searches were performed in English and Italian. The retrieved material was read and current concepts and common problems, hopes and views were synthetized.

For the literature review, we reviewed studies from the systematic review on effectiveness and safety (see Chapter 4) focusing on those which measured quality of life with a standardized instrument in our target population, regardless of study design.

To elicit expert opinions we contacted the Director of the Psychoncological Service of the National Cancer Institute Regina Elena in Rome and asked for availability for interview. She and her staff[1] had a direct experience with our target population: radioembolisation is used in her center and the group conducted the study on QoL with SIRT for patients with CRC liver metastasis within the Cosimelli et al. study (2010).

7.3 Results

We could find very few *spontaneous narratives on the internet*. The percentage of patients being treated with SIRT is small and the percentage of them who end up by making her/his voice heard on the internet via forum or blogs is even smaller (see Appendix 10 for the list of consulted websites). We had to rely above all on Anglophone internet sources because although there are various websites in Italian, there were few direct contributions from Italian oncological patients and even fewer from patients with liver metastasis that had SIRT as a second and further line

[1]Dr.PatriziaPugliese, Director of the Psycho-Oncological Service at Regina Elena Tumor Institute of Rome, Dr. Maria Perrone and Dr. Chiara Falcicchio from Regina Elena Psycho-Oncological Service.

treatment. Anglophone websites and forums had much more discussions and view exchanges on therapies, life with cancer and side effects of therapies. Furthermore in Italy patients and their associations seem to not have acquired the same positive attitude toward this kind of communication channels/means. From what we could understand, this treatment is obviously perceived as a salvage one and patients are very positive and have high expectations. Physical symptoms related to it are the ones which are mostly reported in patients' descriptions, while no mention is made of other aspects (e.g. safety for patient and its importance to others).

For *the literature review* the 30 studies selected to be read in full text within the systematic review were screened and we focused on those that measured QoL with SIRT in CRC patients with liver metastasis regardless of study design. Only the study by Cosimelli M et al. 2010, which is a non-randomized multicenter study measured this outcome. The study authors provide a very short description of QoL outcome in the publication. They administrated cancer and site- specific questionnaires to 14 patients (out of 50 patients who were included in the study) before treatment and after 6 weeks. The interpersonal and technical skills of healthcare operators and the information they provided on treatment were evaluated and the authors state they were judged good by patients (EORTC IN – PATSAT 32) . Compliance was good (mean 8 out of a 10 point scale, were 10 is the maximum score). Anxiety and depression levels before treatment were borderline, but anxiety decreased significantly after 6 weeks, while the depression score did not change. According to the authors the results show good overall QoL with SIRT.

The lack of a comparator in this study does not allow us to assess how much better or worse QoL with SIRT would be compared to an alternative.

As regard to the *interview with experts,* our aim during the interview was to collect information on expectations, views, hopes of patients with CRC who undergo radioembolisation and to obtain more information and data on QoL with SIRT as measured during the Cosimelli et al study, since the published study provided a very short description of results for this outcome.

Experts agreed as follows:

- The oncological patient who undergoes radioembolisation for liver metastasis is usually one who is adaptive: this is probably due to the fact that the patients have already undergone many psychological changes from the first diagnosis of cancer to metastasis, and from several chemotherapy cycles (some of them are usually 8-9 chemotherapy cycles).
- Expectations on this therapy are high with a positive effect on treatment compliance .
- The patient perceived the treatment as salvage.
- Better information and communication about treatment positively affects compliance.

We then asked experts for more information about the quality of life as measured within the Cosimelli et al study.

They explained that patients who were enrolled at the time in this QoL survey were just the 14 from the Regina Elena center, as this was the only center - among those involved in this multicenter trial - which had a psycho-oncological service. Before undergoing SIRT a semi structured interview was done with each single patient. They were asked to fill 5 questionnaires: EORTC QLQ C 30, EORTC QLQ CR 38, HADs, EORTC IN-PATSAT32 and QLQ LMC 21. Patients were given questionnaires before treatment (T0) and after 6 weeks (T1). As already said, the first is a questionnaire developed to assess the quality of life of oncological patients which has been translated and validated into 81 languages. The EORTC QLQ CR 38 is its "disease specific" module for colorectal, the EORTC in-PATSAT32 a general questionnaire for satisfaction with care, the Hospital Anxiety and Depression scale (HADs) is a fourteen-item scale that measures the patient's level of anxiety and depression and the EORTC QLQ LMC 21 a specific module for colorectal liver metastases: the experts explained that, although they decided to used it, at the time of the study this instrument had not been yet validated.

We asked for more information on results from EORTC QLQ C 30 and EORTC QLQ CR 38, while we did not focus on QLQ LMC 21 as this instrument was not yet validated when used within the study and on EORTC IN-PATSAT 32 and HADs as the data about it provided in Cosimelli et al were exhaustive, given our objectives.

The EORTC QLQ C 30 and QLQ CR 38 results showed an overall stable trend in every functional scales, apart from some dimensions such as the "Emotional State", where average scores showed a better/positive trend. For symptom scales such as "Fatigue" the average scores did not register significant changes, apart from the dimension "Pain" which was slightly worse after the treatment[2]. As a whole, results from EORTC QLQ C 30 and QLQ CR 38 show no significant changes and experts final evaluation was that QoL as measured by cancer and site specific questionnaires was not adversely affected by radioembolisation[3].

7.4 Conclusions

From the patients' point of view, being able to undergo radioembolisation means having a further chance. The attitude toward it is usually positive and probable side effects are regarded as tolerable. Although the study by Cosimelli et al. is not randomized and not comparative, available data would indicate that QoL is not negatively affected by the use of SIRT.

Any future study comparing radioembolisation with other therapies should always include QoL as a secondary outcome measured with standardized and internationally validated instruments.

[2]Osaba et al. highlights that a difference of three points in the average scores on a dimension has to be interpreted as no change/stability. The difference has to be at least of 5 points to be significant form a clinical point of view (Osaba et al. 1998).

[3]Dr. Tiziana Pugliese revised and co-wrote this section. We thank Dr. Maria Perrone and Dr. Chiara Falcicchio who kindly sent us more information about the questionnaires used to measure QoL with SIRT and helped to clarify doubts on data interpretation.

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8. Discussion

The results of our systematic review show that the combination of SIRT with chemotherapy vs. chemotherapy alone for the treatment of colorectal liver metastases may have a potential benefit in terms of shortened time to liver progression (TTLP) and time to disease progression (TTDP) of around 3 months.

However, these results come from the single trial identified in our systematic review (Hendlisz 2010) with a limited number of participants (n=46).

The results of our survey of harms of SIRT show that pain and fever are the most common side effects experiences reported. However, these events could be also be interpreted as a good response to the treatment because they may be induced by tumour necrosis.

Our survey shows a scatter of many different Italian Hospital Centres performing SIRT on a small number of cases. In some cases these may have been part of study protocols for formal scientific investigations. This may explain the irregular pattern of provision of the therapy. In other cases sporadic use may be a response to external pressures. A more rational use of resources would involve concentration of all patients in a smaller number of qualified Hospitals doing higher volumes of SIRT and accruing experience with the technique.

Notwithstanding the publication in the next few years of large datasets from trials nearing completion (see Chapter 4), we think SIRT treatment for liver metastases of colorectal carcinoma is a promising technique which needs further development and assessment within formal protocols of randomised controlled trials. These should be conducted by a network of centres probably at European or Global level. Of note however is that the evidence from some trials is likely to be of limited use when published. For example the comparator in trial NCT00199173 is infusional intravenous (IV) 5FU, an obsolete form of chemotherapy. This is probably a reflection of the age of the trial (first registered in 2005, completed in 2010 and never published) (http://clinicaltrials.gov/ct2/show/record/NCT00199173).

The absence of economic studies of SIRT use in our evidence review may be partly justified by the lack of effectiveness evidence. The only effectiveness study included did not have sufficient data to carry out a robust economic evaluation. The potential costs of SIRT should require an exhaustive and complete economic evaluation in terms of cost per outcome (survival and QALY) compared with standard interventions to guarantee the best evidence base for decision-making.

Data from our context analysis showed a complexity of organization and management aspects due to the variety in professionals, skills, and equipment involved. Costs estimates from our survey reflect this complexity. The high cost of the single dose (10,000 euros) and the absence of a

treatment code in the classification of procedures in use, make the creation of a national fee necessary. The total costs per procedure estimated in this report (Euros 15,229) are higher than those reimbursed (using different codes) to hospitals.

The finding that 10 years after the approval of the technique for such a late and intractable form of cancer, evidence of its effects is thin and its effects on quality of life are almost unknown.

Given the potential large costs of the intervention if widely adopted and the apparently promising nature of its effects on life, its quality and its acceptability to vulnerable patients, further evidence is required.

9. Recommendations

We recommend that the results of completed and nearly completed trials currently still active be reported at the earliest opportunity. Ideally this could be done directly as preliminary summary results on the clinicaltrials.gov website.

Given the nature and stage of the illness, the potentially high costs of SIRT and the uncertainty surrounding its effects, the adoption of SIRT would be recommended in few selected cases.

10. Funding

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Agenas takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of the Italian MoH or any regional government.

11. Competing interests declaration

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the Agenas authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document. M Cosimelli is coordinator and scientifc responsible of the clinical study IFO-SITILO SIRKRAS ("Studio multicentrico SIRKRAS di fase II randomizzata su chemioterapia sistemica versus chemioterapia sistemica più Radioterapia interna Selettiva - SIRT - nelle metastasi epatiche colorettali non resecabili con mutazione del gene RAS"), recently approved by the IFO Ethical Committee. The SIRKRAS study is supported by a grant per patient of euros 5,500 provided by SIRTEX to the participating centres enrolling eligible patients in this study.

V Mazzaferro received honoraria to speak at scientific symposia and training courses organised at the National Cancer Institute of Milan and abroad from an international specialist healthcare company developing and commercializing radioactive beads.

Appendix 1 - Literature search strategy on effectiveness and safety

Search strategy: PUBMED

SIRT "[Title/Abstract]) OR " Selective Internal Radiation Therapy" "[Title/Abstract]) OR Radioembolization "[Title/Abstract]) OR "Radio embolization" [Title/Abstract])	AND	"colorectal neoplasms"[MeSH descriptor explode all trees] OR " "Colorectal neoplasm*"[Title/Abstract]	AND	("Liver neoplasms [MeSH descriptor explode all trees] OR "Liver neoplasm*"[Title/Abstract] OR Liver metastases [Title/Abstract]

Population: patients (aged 18-80) ; COMPARATIVE STUDIES , REVIEW, SYTEMATIC REVIEW, COST EFFICACY STUDIES.

Search strategy: EMBASE

Sirt:ab,ti OR 'selective internal radiation therapy':ab,ti OR radioembolization:ab,ti OR 'radio embolization':ab,ti	AND	"colorectal neoplasms [MeSH descriptor explode all trees] OR " "Colorectal neoplasm*":ab,ti	AND	("Liver neoplasms [MeSH descriptor explode all trees] OR "Liver neoplasm*:ab,ti OR Liver metastases :ab,ti OR "Liver metastases" de, syn, Keyword Or "Liver neoplasms" de, syn, Keyword

Population: adult patient (age 18-80); COMPARATIVE STUDIES , REVIEW, SYTEMATIC REVIEW, COST EFFICACY STUDIES.

DARE ALL DATABASES

Search strategy: COCHRANE

Sirt: *title abstract keywords* OR 'selective internal	AND	"colorectal neoplasms" *title abstract keywords* OR	AND	("Liver neoplasms" *title abstract keywords*]) OR "Liver neoplasms" [MeSHdescriptor explode

radiation therapy': *title abstract keywords* OR radioembolization: *title abstract keywords* OR 'radio embolization':*title abstract keywords*		"colorectal neoplasms" [MeSH descriptor explode all trees]		all trees] OR "Liver neoplasm*: *title abstract keywords* OR Liver metastases : *title abstract keywords*

Population: adult patient (age 18-80); COMPARATIVE STUDIES, REVIEW, SYTEMATIC REVIEW, COST EFFICACY STUDIES.

1 item at 1/2/2013

Search strategy: http://www.clinicaltrial.gov

Advanced search:	
Conditions	Interventions
liver metastases	*radioembolization*
	*Sir Spheres**
	*Therasphere**
	Yttrium 90

Accessed on 5 June 2013

Appendix 2 - Data Extraction Sheet

PART 1

Background Information and Description of study

Reviewer:
Study unique identifier:
Published: Y/N
Reference: (If applicable)
Period study conducted:
Abstract/Full paper
Country or countries of study:
Number of studies included in this paper:
Funding source (delete non applicable items):
Government , Pharmaceutical, Private, Unfunded, Unclear
Paper/abstract numbers of other studies with which these data are linked:
Reviewer's assessment of study design (delete non applicable items):

Study Category	Study Design		
Experimental	RCT/CCT	HCT	X crossover RCT
Non-randomised analytical (specifically designed to assess association)	Prospective/Retrospective Cohort	Case Control	X sectional
Non-randomised comparative (not specifically designed to assess association)	Case X Over/Time series	Ecological study	Indirect Comparison (Before and after)
Non-comparative	EXCLUDE		

Does the study present data distributed by age group/occupation/health status?

		Sub group distribution	
		Yes	No
Age group			
Occupation			
Health status			
Gender			
Risk group			

Description of study

Methods

Participants

Interventions/Exposure

Outcomes

Effectiveness

Safety

Notes
The authors conclude that

PART 2a

Methodological Quality Assessment

RCT and CCT only

Generation of allocation schedule (delete non applicable items):

a) random number tables
b) computer random-number generator
c) coin tossing
d) shuffling of allocation cards
e) any other method which appeared random

Concealment of treatment allocation (delete non applicable items):

a) there was some form of centralised randomization scheme where details of an enrolled participant were passed to a trial office or a pharmacy to receive the treatment group allocation.
b) treatment allocation was assigned by means of an on-site computer using a locked file which could be accessed only after inputting the details of the participant.
c) there were numbered or coded identical looking compounds which were administered sequentially to enrolled participants;
d) there were opaque envelopes which had been sealed and serially numbered utilised to assign participants to intervention(s)
e) a mixture of the above approaches including innovative schemes, provided the method appears impervious to allocation bias.
f) allocation by alternation or date of birth or case record or day of the week or presenting order or enrolment order.

[Concealment methods are described as "adequate" for (a), (b), (c), (d) or (e). Method (f) is regarded as "inadequate".

Exclusion of allocated participants from the analysis of the trial

a) Did the report mention explicitly the exclusion of allocated
b) participants from the analysis of trial results?
c) If so did the report mention the reason(s) for exclusion? (if yes, specify)

Measures to implement double blinding

a) Did the report mention explicitly measures to implement and protect double blinding?
b) Did the author(s) report on the physical aspect of compound administration - (i.e. appearances, colour, route administration)

PART 2b

Description of interventions and outcomes

RCT and CCT only

Intervention tested

	Intervention and composition	Product and manufacturer	Schedule & dosage and status	Route of administration
Arm 1				
Arm 2				
Control				

Notes:

- index intervention goes in the Arm 1 line, Placebo in the last line

Details of Participants

	Enrolled	Missing	Reasons	Inclusion in analysis	Notes
Active arm 1					
Active arm 2					
Controls					

Outcomes List – Effectiveness

Outcome	How defined	Description/Follow-up/Notes

Outcomes List - Safety

Outcome	How defined	Description/Follow-up/Notes

Investigators to be contacted for more information? Yes No

Contact details (principal investigator, fill in only if further contact is necessary):

PART 2c

Data Extraction and manipulation

(to be used for dichotomous or continuous outcomes)

RCT and CCT only

Comparison

Outcomes	n/N Index Arm	n/N Comparator

Notes (for statistical use only)

Appendix 3 - List of the background references

ASERNIP – Systematic Review of Radiofrequency ablation for the treatment of liver tumours. NO. 140. August 2006.

Belinson S, Chopra R, Yang Y, Shankaran V, Aronson N. Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer. Comparative Effectiveness Review No. 93. (Prepared by Blue Cross and Blue Cross Blue Shield Association Technology Evaluation Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC014-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012.

NICE National Institute for Health and Clinical Excellence - Interventional Procedure. Interventional procedure overview of selective internal radiation therapy for non-resectable colorectal metastases in the liver. National Institute for Health and Clinical Excellence - Interventional Procedures. PDF document .

Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev. 2009; (4):CD007045.

Appendix 4 - Included study

Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J ClinOncol. 2010 Aug 10; 28(23):3687-94.

Appendix 5 - List of excluded studies and reasons of exclusion

First line study

Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J SurgOncol. 2004 Nov 1; 88(2):78-85.

Non comparative studies

Cianni R, Urigo C, Notarianni E, et al. Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. CardiovascInterventRadiol. 2009 Nov;32(6):1179-86. PMID: 19680720.

Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010 Jul 27;103(3):324-31. PMID: 20628388

Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectablechemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. Radiology. 2008 May;247(2):507-15. PMID: 18349311.

Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer. 2009 May 1;115(9):1849-58. PMID: 19267416.

Moroz P, Anderson J E, Van Hazel G, et al. Effect of selective internal radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume. J SurgOncol. 2001 Dec; 78(4):248-52.

Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J VascIntervRadiol. 2008 Aug;19(8):1187-95. PMID: 18656012.

Jiao LR, Szyszko T, Al-Nahhas A, et al. Clinical and imaging experience with yttrium-90 microspheres in the management of unresectable liver tumours. Eur J SurgOncol. 2007 Jun;33(5):597-602. PMID: 17433608.

Lim L, Gibbs P, Yip D, et al. A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer. 2005;5:132. PMID: 16225697.

Salvage studies

Martin LK, Cucci A, Wei L, et al. Yttrium-90 radioembolization as salvage therapy for colorectal cancer with liver metastases. Clin Colorectal Cancer. 2012 Jan 23PMID: 22277350.

Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J VascIntervRadiol. 2009 Mar;20(3):360-7. PMID: 19167245.

Dose escalation study

Van Hazel G A, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J ClinOncol. 2009 Sep 1; 27(25):4089-95.

Not a systematic review

Vente M A, Wondergem M, van der Tweel I, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. EurRadiol. 2009 Apr; 19(4):951-9.

Not primary CRC

Gulec S A, Pennington K, Wheeler J, et al. Yttrium-90 Microsphere-selective Internal Radiation Therapy With Chemotherapy (Chemo-SIRT) for Colorectal Cancer Liver Metastases: An In Vivo Double-Arm-Controlled Phase II Trial. Am J ClinOncol. 2012 Jun 14.

All-lines of treatment study with no data breakdown by line, treatment doses are much higher than presently administered

Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, Gebski V. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Annals of Oncology 2001;12:1711–1720.

Appendix 6 - Questionnaire for the survey

QUESTIONARIO

SelectiveinternalradiationtherapY

Versione 4.2 (11 febbraio 2013)

Ente

Sezione A – Informazionisullastruttura

Indirizzo	
Regione	

Responsabilearruolamentoclinico	……	Telefono	
		E-mail	

Responsabilecentroradiologiainterventistica	……	Telefono	
		E-mail	

ResponsabiledellaMedicinaNucleare	……	Telefono	
		E-mail	

Responsabilecompilazione	……	Telefono	
		E-mail	

Tipo di ente/centro	**Pubblico**	**Privato**	**PrivatoConvenzionato**

	☐ Ospedaliero	☐ Ospedaliero	☐ Ospedaliero
	☐ Ambulatoriale	☐ Ambulatoriale	☐ Ambulatoriale
	☐ Altro-Specificare:	☐ Altro-Specificare:	☐ Altro-Specificare:

Quali delle seguenti unità operative sono presenti nella sua struttura?	
☐ Radiologia	☐ MedicinaNucleare
☐ Radiologiainterventistica	☐ Oncologia
☐ Emodinamica	☐ Chirurgia

Quali delle seguenti tecnologie sono presenti nella struttura?	
☐ TC	☐ Angiografo
☐ Gamma Camera	
☐ PET/TC	

Sezione B – Informazionisullatecnologia

B.1. Indicare la data di inizio utilizzo della radioembolizzazione nella sua struttura
_____/_____/_____

B.2. Qual è l'ambito di utilizzo della radioembolizzazione nei pazienti con CRC?
☐ Sperimentazioneclinica
☐ Praticaclinica

B.3. Indicare la tecnologia utilizzata:		
Produttore	☐ ®SIR-Spheres	☐ Terasphere®
Fornitore		
Modello		
Anno di sottoscrizione del contratto e primo utilizzo		
Modalità di acquisizione (acquisto, service, ecc.)		
Duratacontrattuale (in mesi)		
Importototale del contratto		
"Dose size" richiesta per ogni spedizione		
N. di dosipreviste		
Attività (Bq) di ciascuna dose		
Attività (Bq) media somministrata per ciascun trattamento dei pazienti con CRC		
Costodella dose		
Costounitario per Bq		
Altreattrezzature (specificare):		

*indicare solo se si ha un prezzo unico per tutte le componenti (^{90}Y, tecnologia per la somministrazione, consumabili, ecc.)

Sezione C – Informazioni cliniche sui pazienti

Le informazioni richieste in questa sezione dovrebbero essere desunte dai dati relativi ai pazienti trattati nell'anno 2012. Nel caso la sua struttura non disponesse di dati per questo anno, indichi qui a quale anno si riferiscono

Anno_____

C.2. Qual è il numero totale di pazienti trattati	☐ ®SIR-Spheres	☐ Terasphere®
N° pazienti in prima linea di trattamento		
N° pazienti in seconda linea di trattamento e oltre		
N° pazienti trattati a scopo "compassionevole"		

C.3. Specificare il numero di pazienti con CRC trattati con radioembolizzazione in ciascuna delle seguenti linee di trattamento	☐ ®SIR-Spheres	☐ Terasphere®
Pazienti in prima linea di trattamento		
Pazienti in seconda linea di trattamento e oltre		
Pazienti trattati a scopo "compassionevole"		
Totale pazienti con CRC trattati con radioembolizzazione		

C.4. In quante sedute è stato somministrato il trattamento?	☐ 1	☐ 2	☐ > 2

C.5. Qual è l'intervallo fra i due trattamenti	_____ gg.

C.6. Se sono presenti lesioni sui due lobi vengono trattate nella stessa seduta?	☐ Si	☐ No

C.7. Quali sono le caratteristiche di eleggibilità a radioembolizzazione dei pazienti con CRC?		
Coinvolgimento epatico (indicare il numero di segmenti residui alla resezione e il valore %)	N°:	%:
Numero di metastasi extra-epatiche	N°:	
Numero di metastasiepatiche	N°:	
Linee di chemioterapia somministrata (max, min, mediana)	max____ min ____	mediana
Bilirubinemia (valori max, min e mediani)	min max mediana	INR Piastrine
Anomalievascolari		
Precedentiresezioniepatiche	N°:	
Leakage extraepatico	%	

C.8. Indicare il numero di pazienti per fascia di età e sesso con CRC trattati con radioembolizzazione	®SIR-Spheres		TheraSphere®	
	M	F	M	F
<18 anni				
18-80 anni				
>80 anni				

Sezione D – Informazioni cliniche sul trattamento

D.1. La radioembolizzazione viene utilizzata in aggiunta al trattamento chemioterapico?	SI	NO
Prima linea		
Seconda linea		
Terza linea		
Quarta linea		

D.2. Le dosi e il numero di cicli di chemioterapia somministrate ai pazienti che eseguono la radioembolizzazione sono uguali nel caso del solo trattamento chemioterapico?	SI	NO
Prima linea	☐ Cicli☐ Dose	☐ Cicli☐ Dose
Seconda linea	☐ Cicli☐ Dose	☐ Cicli☐ Dose
Terza linea	☐ Cicli☐ Dose	☐ Cicli☐ Dose
Quarta linea	☐ Cicli☐ Dose	☐ Cicli☐ Dose

D.3. Quali farmaci (o combinazioni di farmaci) sono utilizzati per il trattamento chemioterapico in aggiunta alla radioembolizzazione? (indicare anche la linea di trattamento)	Linea di trattamento (I, II, III IV)	Farmaco utilizzato (nomecommerciale)	Dose per ciclo (indicare la dose media per singolo farmaco)	Numero di cicli	Costo di aggiudicazione per farmaco utilizzato
Oxaliplatin					
Irinotecan					

5-FU					
Leucovorin Calcium (LV)					
Capecitabina					
Mitomicina					
Bevacizumab					
Cetuximab					

D.4. Quali altre procedure vengono effettuate ai pazienti con metastasi epatiche da CRC prima e dopo il trattamento con radioembolizzazione (descrivere)

D.5. Indicare le complicanze, e la loro ricorrenza, in seguito alla somministrazione del trattamento con SIRT nei pazienti con CRC	
	N di ricorrenze
Doloreincoercibile post SIRT	
Insufficienzaepatica	
Ulceregastroduodenali	
Alterazioni stabili (> 7 giorni) della funzione epatica	
Febbre>38° C	
Altro (indicare)	

D.6. Dati di outcome	
Risposte cliniche (CR, PR, SD, PD)* sul totale dei pazienti indicati nella tabella C3	Distribuzione %
	CR =
	PR =

	SD =
	PD =
Sopravvivenzamediana (mesi)	
Viene rilevata la qualità di vita dopo SIRT?	☐ Si ☐ No

*CR= risposta completa; PR= risposta parziale; SD= risposta stabile; PD= progressione di malattia

D.7. Se si sono verificate complicanze, indicare quante hanno determinato un intervento in regime:		
☐ Ambulatoriale	☐ Day Hospital	☐ Ricov. Ordinario

D.8. Indicare l'attività media (espressa es. in Bq) necessaria per il singolo trattamento del paziente con CRC	

Sezione E – Informazioni sull'organizzazione e sui costi della procedura

Work up diagnostico pre-radioembolizzazione

E.1. Qual è il numero di pazienti e delle prestazioni effettuate e il costo degli esami di Work up diagnostico alla radioembolizzazione?	Codice prestazione di specialistica ambulatoriale	Numero di pazienti	N di esami effettuati	Costo unitario
Ecografia epatica				
Ecografia epatica intraoperatoria				
TC con volumetria epatica				

CEA e CA 19.9				
PET				
Prima arteriografia arteria epatica e mesenterica + scintigrafia con MMA				
Altro (specificare)				

E.2. Indicare le risorse impiegate nel work up diagnostico	Numero di personale impiegato per procedura	Tempo impiegato (per procedura) (minuti)
Medico nucleare		
Oncologo		
Radiologo interventista		
Fisico medico		
Infermiere		
Medico patologo (consulto)		
Psicooncologo		
- Altro (specificare)		

E.3 Risorse impegnate	Tempo di occupazione sala angiografica	Costo unitario
Sala angiografica		
Spirali biocompatibili	Numero	
Degenza in ospedale	gg di degenza	
Altro (indicare)		

Trattamento

E.4. Indicare il numero di pazienti e delle prestazioni effettuate e il costo degli esami della radioembolizzazione (trattamento)	Codice prestazione di specialistica ambulatoriale	Numero di pazienti	N di esami effettuati	Costo unitario
- Arteriografia				
- Iniezione della dose				
- Altro (specificare)				

E.5. Indicare le risorse impiegate nel trattamento	Numero di personale impiegato per procedura	Tempo impiegato (minuti)
Medico oncologo		
Medico nucleare		
Fisico medico		
Radiologo interventista		
Infermiere		
Psico oncologo		
- Altro (specificare)		

E.6. Risorse impegnate	Tempo	Costo
Occupazione della sala angiografica (Espressa in minuti)		
Permanenza in ospedale (Espresso in giornate		

di degenza)		
Altro (specificare)		

Follow up

E.7. Costo esami radioembolizzazione (follow up)	Codice prestazioni specialistica ambulatoriale (Ministero Salute)	Numero di pazienti	N di esamie ffettuati	Costo unitario
Esami del sangue				
CEA				
CT				
Visita con specialista				
- Altro (specificare)				

E.8. Indicare le risorse impiegate nel follow up	Numero di personale impiegato per procedura	Tempo impiegato (minuti)
Medico oncologo		
Medico nucleare		
Fisico medico		
Radiologo interventista		
Infermiere		
Psico oncologo		
- Altro (specificare)		

E.9. Qual è la modalità di rimborso della prestazione?
☐ DRG (specificare il codice e l'importo)
☐ Fondi di ricerca
☐ Altro (specificare)

E.10. Quali attività comprende l'eventuale rimborso?
☐ Work up diagnostico pre-radioembolizzazione
☐ Trattamento
☐ Follow-up

Appendix 7 - Centers performing radioembolization in Italy

Hospital Center	City
Ospedale Santa Maria Goretti	Latina
Istituto Regina Elena – IFO	Roma
Istituto Nazionale Tumori di Napoli - IRCCS "Fondazione G. Pascale"	Napoli
Policlinico S. Orsola Malpighi	Bologna
Azienda Ospedaliero Universitaria di Udine	Udine
Azienda UlSS 9 di Treviso - Ospedale S. Maria di Ca' Foncello	Treviso
Ospedale Di Circolo e Fondazione Macchi	Varese
Azienda Ospedaliera Ordine Mauriziano	Torino
Casa di Cura Pio XI	Roma
Istituto Europeo di Oncologia (IEO)	Milano
AziendaOspedaliera "San Gerardo"	Monza
Azienda Ospedaliera – Ospedale Niguarda Ca' Granda	Milano
Fondazione IRCCS Istituto Nazionale Tumori (INT)	Milano
Policlinico Universitario "Agostino Gemelli"	Roma
Azienda Ospedaliero Universitaria – Stabilimento di Cisanello	Pisa
Azienda Sanitaria Ospedaliera S. Croce e Carle	Cuneo
Azienda USL Valle d'Aosta	Aosta
IRCCS Ospedale Casa Sollievo della Sofferenza	S G Rotondo
Azienda Ospedaliera Ospedale Riuniti di Bergamo	Bergamo

Appendix 8 - Search strategy for the systematic review of economic studies

PICO:

Population: patients (aged 18-80) with non-resectable liver metastases from CRC

Intervention: Selective Internal Radiation Therapy (SIRT)

Comparator: Chemotherapy at 2nd and later lines

Outcomes: economic evaluation studies on selective internal radiation therapy for liver metastases from primary colorectal adenocarcinoma.

Eligibility criteria

Study design: comparative studies, systematic review, non systematic review.

Language: English, French

Publication date: 2000- to date

Inclusion criteria

The inclusion criteria will be: economic evaluations based on all types of economic analysis (CEA, CUA, CBA; CCA; CMA) comparing the use of radioembolization with standard chemotherapeutic treatment from 1997 to date.

Databases

Medline, Embase, Cochrane Library, DARE all databases; Agency for Healthcare Research and Quality (AHRQ); Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP-S) , Health Canada; International Network of Agencies for Health Technology Assessment (INAHTA); Medical Services Advisory Committee (MSAC); National Coordinating Centre for Health Technology Assessment (NCCHTA); National Horizon Scanning Centre ; National Institute for Health and Clinical Excellence (NICE); NHS Quality Improvement Scotland (NHS QIS) , Nice, Trip database, Clinicaltrials.gov, Cancer.gov

Search strategy:MEDLINE

SIRT "[Title/Abstract]) OR " Selective Internal Radiation Therapy" "[Title/Abstract]) OR "selective internal radio therapy" OR Radioembolization" [Title/Abstract]) OR "Radio embolization"[Title /Abstract])	AND	"colorectal neoplasms"[MeSH descriptor explode all trees] OR " "Colorectal neoplasm*"[Title/Abstract] OR "Colorectalcarcinoma*"[Title/Abstract] OR "Colorectal tumor*"[Title/Abstract]	AND	("Liver neoplasms[MeSH descriptor explode all trees] OR "Liver neoplasm*"[Title/Abstract] OR "Liver metastases" [Title/Abstract]	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost – effectiveness [Title/Abstract] OR Cost – utility [Title/Abstract]OR Cost*[Title/Abstract]

2 items at 1/2/2013

Search strategy:EMBASE

Sirt:ab,ti OR 'selective internal radiation therapy':ab,ti OR radioembolization:ab,ti OR 'radio embolization':ab,ti	AND	"colorectal neoplasms [MeSH descriptor explode all trees]OR " "Colorectalneoplasm*": ab,ti OR "Colorectal carcinoma*":ab,ti OR "Colorectal tumor*":ti,ab OR "Colorectal neoplasm*":de, syn, keyword OR "Colorectal carcinoma*":de, syn, keyword OR "Colorectal tumor*": de, syn, keyword	AND	("Liver tumor" EMTREE descriptor explode all trees]OR "Liver neoplasm*:ab,ti OR Liver metastases :ab,ti OR HCC:ab,ti OR "hepatocellularcancer":ti,ab OR "Hepatocellular carcinoma":ti,ab OR "Liver metastases"de, syn, Keyword OR "Liver neoplasms" de, syn, Keyword OR HCC: de, syn, KeywordOR "hepatocellular cancer":de, syn, Keyword OR "Hepatocellular carcinoma": de, syn, Keyword	"Costs and Cost Analysis/:ab,ti OR "Economics"/:ab, ti OR "Cost Allocation"/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/:ab,ti OR "Cost Saving"/:ab,ti OR Cost*/:ab,ti OR "Cost-effectiveness"/:ab,ti OR "Cost-utility"/:ab,ti OR

2 items at 1/2/2013

Search strategy:DARE AND ALL DATABASES

Sirt:*title abstract keywords* OR 'selective internal radiation therapy': *title abstract keywords*	AND	"colorectal neoplasms" *title abstract keywords* OR "colorectal neoplasms" [MeSH descriptor explode all trees]	AND	"Liver neoplasms" *title abstract keywords*] OR "Liver neoplasms"[MeSH descriptor explode all trees] OR "Liver neoplasm*: *title*	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR

OR radioembolization: *title abstract keywords* OR 'radio embolization': *title abstract keywords*				*abstract keywords* OR Liver metastases : *title abstract keywords* OR "hepatocellular cancer": *title abstract keywords* OR "Hepatocellular carcinoma": *title abstract keywords* OR HCC: *title abstract keywords*	"Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR "Cost-effectiveness" (ti,ab,kw) OR "Cost-utility" (ti,ab,kw) OR "Cost – effectiveness" OR Costs (ti,ab,kw) OR Cost (ti,ab,kw) OR Economic (ti,ab,kw)

4 items

Appendix 9 - List of excluded studies from the economics review

ASERNIP - S. Radiofrequency ablation for the treatment of liver tumours. 140.

MSAC application 1034. Selective Internal Radiation Therapy for Hepatic Metastases using SIR Spheres. March 2002.

MSAC application 1082. SIR-Spheres for the treatment of non-resectable liver tumours. August 2005.

Ray, C. E. Jr; Battaglia, C.; Libby, A. M.; Prochazka, A.; Xu, S., and Funaki, B. Interventional radiologic treatment of hepatocellular carcinoma-a cost analysis from the payer perspective. J Vasc IntervRadiol. 2012 Mar; 23(3):306-14.

Whitney, R.; Valek, V.; Fages, J. F.; Garcia, A.; Narayanan, G.; Tatum, C.; Hahl, M., and Martin, R.C. 2nd.Transarterial chemoembolization and selective internal radiation for the treatment of patients with metastatic neuroendocrine tumors: a comparison of efficacy and cost. Oncologist. 2011; 16(5):594-601.

Appendix 10 - List of consulted web sites

Patients associations/oncological associations web sites and forums

Associazione italiana ricerca sul cancro (AIRC), Web: www.airc.it. Accessed 15th January 2013

Associazione nazionale tumori ONLUS (ANT), Web: www.antnet.it. Accessed 15th January 2013

Associazione italiana malati di cancro parenti ed amici (AIMAC), Web: www.aimac.it. Accessed 15th January 2013

Associazione nazionale guariti o lungo viventi ONLUS (ANGOLO), Web: http://www.associazioneangolo.it. Accessed 15th January 2013

Federazione italiana delle associazioni di volontariato in oncologia (FAVO), Web: www.favo.it. Accessed 15th January 2013

Lega italiana per la lotta contro i tumori (LILT), Web: www.legatumori.it. Accessed15th January 2013

Vida, Web: www.vidas.it. Accessed 18th January 2013

Associazione italiana tumori gastro-intestinali (AIG), Web: www.gistonline.it. Accessed 18th January 2013

Associazione nazionale volontari lotta contro i tumori (ANVOLT), Web: www.anvolt.it. Accessed18th January 2013

Associazione malati oncologici onlus, Web: www.associazionemalationcologici.org. Accessed 18th January 2013

Cancer Carehttp://cancer.about.com. Accessed 22th January 2013

The Cancer Survivors Network, Web: http://csn.cancer.org/ . Accessed 22th January 2013

Voiceofsurvivors.org. Accessed 22th January 2013

www.fightcolorectalcancer.org. Accessed 22th January 2013

www.cancertodaymag.org.Accessed22th January 2013

www.canceradvocacy.org/living-with-cancer/survivor-stories/suzanne-lindley.html. Accessed22th January 2013

www.inspire.com/groups/advanced-breast-cancer/discussion/liver-mets-successful-results-using-sirs/. Accessed 22th January 2013

Forum http://lavecchiataverna.forumfree.it/http://www.antitalia.org/pubb/forum_amici.php. Accessed22th January 2013

Forum http://www.foruminfocancro.it. Accessed 22th January 2013

Forum http://www.sostumori.org/Documenti/Forum.htm. Accessed 23th January 2013

Forum http://forumtumore.aimac.it/. Accessed 23th January 2013

Forum Cancer Carehttp://cancer.about.com. Accessed 23th January 2013

Forum: www.oncochat.org/Anglophone patients associations/oncological associations web sites and forums. Accessed 23th January 2013

Glossary

Cost effectiveness analysis (CEA), Economic evaluation in which costs and consequences are measured in terms of ratio of a ratio where the denominator is a gain in health and the numerator is the cost associated with the health gain.

Bequerel (Bq), is the unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in witch one nucleus decay per second.

Bremsstrahlung scan, resulting from the interaction of beta particles with tissue, that are sufficiently penetrative for detection by SPECT.

Budget Impact Analysis (BIA) is an estimate of the financial consequences of adoption and diffusion of a health technology within a specific health-care setting or system context given inevitable resource constraints

FDA, Food and Drug Administration

PET–CT, positron emission tomography

PMA, premarket approval application is a kind of approval by FDA for the commercial distribution of the device in accordance with specific conditions

SPECT, Single Photon Emission Computed Tomography