



TITLE: SELECTIVE INTERNAL RADIATION THERAPY OR
RADIOEMBOLIZATION FOR INOPERABLE LIVER METASTASES
FROM COLORECTAL CANCER

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A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of radioembolization for the treatment of metastases to the liver from colorectal cancer. Surgery is the primary treatment of liver metastases, but when surgery is not an option radioembolization may be an attractive alternative.

BACKGROUND

In 2009, the American Cancer Society estimates that there will be 146,970 new cases of colon cancer and 49,920 deaths from colon cancer.¹ Among cancers in the United States, only lung cancer causes more deaths. The liver is the most common site for metastatic colon cancer. Many therapies have been developed to treat liver metastases including surgery, cryoablation, radiofrequency ablation, hepatic arterial chemotherapy (HAC) infusion, trans-arterial chemoembolization (TACE), radioembolization (RE), and external-beam radiation therapy. The only approach shown to cure patients is surgical resection of the metastases, usually in conjunction with neoadjuvant or adjuvant chemotherapy. However, it is not always possible to remove all of the tumors while preserving hepatic function. In some cases, patients initially deemed inoperable are treated with combination chemotherapy and re-evaluated for surgery after chemotherapy.

The primary goal for the treatment of inoperable metastatic colorectal cancer is palliative, not curative. Advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies, have doubled median survival for this population from less than one year to more than two years.²⁻⁵ Systemic chemotherapy is the recommended initial treatment for inoperable metastatic disease and survival benefit has been demonstrated for both second-line and third-line chemotherapy.⁶ Overall survival has been the primary outcome used to assess the value of new chemotherapeutic regimens, though progression free survival usually has correlated with overall survival and quality of life in these studies.^{3,7}

The National Comprehensive Cancer Network (NCCN) recommends against debulking surgery or ablation of metastatic tumors unless done for cure.⁶ However, less than 15% of patients with liver metastases have

operable disease on presentation.⁸ In their first update of the 2010 colon cancer practice guideline, there was no consensus on the appropriate use of other liver directed therapies such as ablation or embolization.⁶

Selective internal radiation therapy (SIRT), aka radioembolization

Liver cells are very sensitive to radiation and this has limited the use of external beam therapy to the liver even with intensity modulated radiation therapy. RE takes advantage of the fact that the blood flow that supports tumors in the liver is primarily from the hepatic artery while blood flow supporting normal liver tissue is primarily from the portal vein.⁹ The most common delivery systems use either glass or resin microspheres impregnated with Yttrium-90, although other radioisotopes have been used. The microspheres are released in the hepatic artery and lodge in the distal arterioles, primarily within tumors. One of the potential benefits is that delivery is not dependant on the number or location of the tumors, because blood will flow from the hepatic artery to tumors even if they were not identified on pre-procedure imaging. Yttrium-90 emits only beta-radiation, which penetrates between three and twelve millimeters into tissue. Thus minimal normal liver tissue surrounding the tumor is affected by the radiation.

RE is normally performed as an outpatient procedure, but requires multidisciplinary treatment planning involving medical oncology, radiation oncology, hepatobiliary surgery and interventional radiology. Prior to the procedure patients usually are required to have a transfemoral hepatic angiogram to assess the arterial supply of the liver with embolization of branches bypassing the liver. This is followed by injection of technetium-labeled macroagglutinated albumin into the hepatic artery with SPECT scanning to evaluate the percentage of injected material shunted to the lungs or gastrointestinal (GI) tract rather than the liver. If the albumin scan indicates that there may be more than 30 Grey of radiation exposure to the lungs or significant flow to the GI tract, then the procedure should not be performed because of the risk of significant radiation pneumonitis and of gastric and duodenal ulceration.¹⁰ It may not be safe to perform the procedure in patients with limited flow through the portal vein, prior radiation therapy to the liver, or limited hepatic reserve.¹⁰

The most common side effects are flu-like symptoms, fatigue, fever, abdominal pressure and nausea. Patients are generally premedicated with corticosteroids and anti-emetic medications to minimize these side effects. More serious adverse events include radiation induced liver disease, radiation pneumonitis from microspheres shunting around the liver and into the lungs, and GI tract ulcerations. Meticulous planning with



pre-procedure angiography, shunt studies, and careful dosimetry has decreased the occurrence of these toxicities.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

SIR-Spheres® (Sirtex Medical Inc., Lake Forest, IL) received FDA Premarket Approval (PMA) clearance on March 5, 2002. SIR –Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

TheraSphere® (MDS Nordion, Inc., Ottawa) received FDA Humanitarian Device Exemption (HDE) on August 11, 1998. TheraSphere is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

.TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “radioembolization,” “SIRT,” “Therasphere,” “SIR-spheres” and “selective internal radiation therapy.” These were cross-referenced with the keywords “liver” and “colorectal”. The search was performed for the period from 1966 through January 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: overall survival, quality of life, and treatment-related toxicities. Progression-free survival and response rates are secondary outcomes of interest.

The search identified 932 potentially relevant trials. After elimination of duplicate and non-relevant references, 86 articles were reviewed in full. A large number of case series were excluded because they were duplicate reports, not report any of the essential clinical outcomes or because they were mixed series of tumors without separate reporting of outcomes for liver metastases from colorectal cancer.¹¹⁻³⁹ The remaining twenty-five references describe two randomized trials^{40, 41}, one small retrospective study comparing RE to chemoembolization (n=36)⁴², and twenty-two case-series.⁴³⁻⁶⁴ The two randomized trials used control groups treated with therapies that are no longer standard today and they were too small (total randomized n = 95) to provide conclusive answers concerning net health outcomes. The search also identified many reviews⁶⁵⁻⁷¹ assessing the role of RE including one recent Cochrane review.⁶⁶

Level of Evidence: 2, 3, and 5.

TA Criterion 2 is not met.

- **In the absence of Level 1 studies, technologies may meet this criterion if, overall, Level 2-4 studies indicate that:**
 - a. The technology provides substantial benefits to important health outcomes and
 - b. The new technology has been shown to be safer or more beneficial than existing technologies or alternative treatments in comparative studies.

TA Criterion 3: The technology must improve net health outcomes.

Case Series

Table 1 summarizes the outcomes from the published case series of RE for the treatment of colorectal cancer metastases to the liver. Patients in these series were an average age of 60 to 65 years old and about one third were women. All had inoperable liver metastases from colorectal cancer. They represented a wide range of patients from those receiving their initial treatment for metastatic colorectal cancer to those who had already failed two or more different chemotherapeutic regimens. The wide variation in outcomes reflects this clinical heterogeneity. The reported response rates varied from 0% to 90% and the median overall survival from the time of RE varied from 4.5 months to 14.5 months. Given that the median overall survival for patients with metastatic colon cancer is now greater than 29 months⁵, these outcomes are not impressive. However, as noted above, all of these patients have inoperable metastases and many have

exhausted first and second line therapies. Thus, their prognosis is worse than the average patient. In order to elucidate the potential value of RE, comparative trials need to be done with clear definition of the patient population and either carefully matched or preferably randomized controls.

Non-randomized, controlled studies

The comparative studies are summarized in Table 2. Hong et al. described a retrospective comparison of RE to TACE as salvage therapy for patients with liver dominant colorectal cancer.⁴² Patients were excluded if they had advanced liver disease (severe ascites, encephalopathy, elevated bilirubin) or had poor functional status (Eastern Cooperative Oncology Group performance status greater than 2). The investigators compared 15 patients treated with RE (age 64 years, 27% female) to 21 patients treated with chemoembolization (age 67 years, 48% female). Approximately 20% of patients in each group had been treated with external beam radiation and radiofrequency ablation. Similarly, about 20% of patients in each group had liver resections prior to the transarterial therapy. All had been treated with modern systemic chemotherapy. The time from diagnosis of liver metastases to the study intervention was 23 months in the RE group and 18 months in the chemoembolization group and extrahepatic metastases were more common in the RE group (43% versus 33%). The chemoembolization drugs included cisplatin, doxorubicin, and mitomycin C. Multiple treatments were performed for 19% of the RE group and 43% of the chemoembolization group. Median overall survival was similar in the two groups: 6.9 months for the RE group and 7.7 months for the chemoembolization group ($p = 0.27$). Overall survival at one, two, and five years was 34%, 18%, and 0% for the RE group and 43%, 10% and 0% for the chemoembolization group. All patients in both groups experienced some minor complications including abdominal pain, nausea, fever, leucocytosis, and fatigue. One patient in the chemoembolization group suffered a pulmonary embolus, but recovered fully. There were no major complications in the RE group.

This was a small, unmatched, retrospective comparison that found no significant differences between two salvage procedures for patients with metastatic colorectal cancer. Because of the small size, the study had limited power to detect any differences between the two procedures. Furthermore, the unmatched, observational study design means that the study is likely subject to selection bias. For instance there were large differences in the proportion of women in the two groups, the presence of extrahepatic metastases, and the proportion of patients with multilobar metastases. It is difficult to draw any meaningful conclusions about health outcomes from this study.

Table 1: Case series describing the outcomes following radioembolization of liver metastases from colorectal cancer

Study Key authors Location	Sphere type	N	Intervention	Response rate, %	Time to progression, months	Median survival, months
Ariel 1982	Yttrium microspheres	40	RE + HAC:	40	NR	29 month average
Anderson 1992	TheraSpheres	7	RE	0	NR	11
Andrews 1994	TheraSpheres	17	RE	29	NR	13.8
Gray 1992	SIR-Spheres	29	RE	45	NR	NR
Stubbs 1999	SIR-Spheres	30	RE	70	NR	6.7
Gray 2000	SIR-Spheres	71	RE	75	NR	9.9
Stubbs 2001	SIR-Spheres	30	RE	73	NR	9.8
Wong 2002	TheraSpheres	8	RE	24	NR	NR
Lewandowski 2005	TheraSpheres	27	RE	35	NR	9.3
Lim 2005	SIR-Spheres	32	RE	31	5.3	NR
Murthy 2005	SIR-Spheres	12	RE + Chemo	0	NR	4.5
Kennedy 2006	SIR-Spheres	208	RE	35	NR	4.5 non-responders 10.5 responders
Mancini 2006	SIR-Spheres	35	RE	12	NR	NR
Stubbs 2006	SIR-Spheres	100	RE + HAC	74	NR	11
Rowe 2007	SIR-Spheres		RE			9.0
Sharma 2007	SIR-Spheres	20	RE+ Chemo	90	9.3	NR
Jakobs 2008	SIR-Spheres	41	RE	17		10.5
Sato 2008	TheraSpheres	51	RE	NR	NR	15 2 year: 27%
Stuart 2008	SIR-Spheres	13	RE		3.7	12
Cianni 2009	SIR-Spheres	41	RE	46	9.2	12
Mulcahy 2009	TheraSpheres	72	RE	40	NR	14.5
Van Hazel 2009	SIR-Spheres	25	RE + Chemo	48%	6.0	12.2

Table 2: Comparative studies of radioembolization of liver metastases from colorectal cancer

Study Key authors Location	Sphere type	N	Study arm: n	Age, yrs Sex, %F	Prior treatment	Response rate	Time to progression, months	Median survival, months	RECIST Grade 3 or 4 Toxicity, n	Quality of life
<u>Randomized trials</u>										
Gray 2001 Australia	SIR-Spheres	70	HAC + RE: 36 HAC: 34	60 23%	14% with prior chemotherapy	44 18 p=0.01	16 10 p=0.001	17 16, p=0.18 2 year: 39% vs. 29%	23 23	Improved in both arms over 18 months. No differences between groups.
Van Hazel 2004 Australia	SIR-Spheres	21	Chemo + RE: 11 Chemo: 10	65 14%	None	78 0	18.6 3.6 p=0.0005	29.4 11.8, p=0.025 2 year: 64% vs. 20%	13 5	No difference at three months, p=0.96.
<u>Comparative study</u>										
Retrospective										
Hong 2009 Baltimore, MD	TheraSpheres	36	RE: 15 TACE: 21	66 39%	100% prior chemotherapy.	NR	NR	6.9 7.7, p=0.27 2 year: 18% vs. 10%	NR	NR

Randomized trials

The first randomized trial of RE was published by Gray et al in 2001.⁴¹ They randomized 74 patients with bilobar, non-resectable liver metastases to monthly HAC with floxuridine or the same therapy plus a single infusion of yttrium-90 microspheres. Recruitment was stopped early (original goal was 95 patients) when the United States Food and Drug Administration indicated that time to disease progression would be an acceptable endpoint for approval of the microspheres. All patients had completed resection of the primary colorectal cancer and had non-resectable metastases limited to the liver or the lymph nodes draining the liver. During the laparotomy for placement of a permanent hepatic artery catheter, extrahepatic metastases were found in four patients. These four patients were ineligible for the trial and were excluded from the published analyses. Of the remaining 70 patients, 36 received RE plus HAC and 34 received HAC alone. The two groups had similar demographics and tumor characteristics including lymph node involvement, tumor differentiation, prior chemotherapy, percentage of liver involvement by the tumor, and time from bowel resection to randomization. The response rate, as measured by tumor area, was greater in patients who received RE (44% versus 18%, $p = 0.01$). The median time to tumor progression using the same standard was also longer in the RE group (15.9 versus 9.7 months, $p = 0.001$). However, overall survival did not differ between the two groups (median 17 months versus 16 months, $p = 0.18$). A post hoc analysis suggested that there may be a survival benefit after 15 months of follow-up. Quality of life generally improved in both groups over the first 18 months of the study and there were no significant differences between the two groups, although none of the data were presented. There were more grade 1 and 2 toxicities in the RE group, primarily due to elevation in liver tests, nausea, and diarrhea. However, the number of grade 3 and 4 toxicities was the same in each group (23 events in each).

The second randomized trial was a phase 2 study published in 2004 by the same research group in Australia.⁴⁰ This trial included patients with bilobar liver metastases from colorectal cancer that could not be treated with surgical resection or any local ablation therapy. In addition, the patients could not have received prior chemotherapy or radiation therapy for the liver metastases. The investigators randomized 21 patients to either systemic chemotherapy with fluorouracil and leucovorin ($n = 10$) or the same chemotherapy plus one treatment with RE on the third or fourth day of the second cycle of chemotherapy ($n = 11$). The two groups had similar demographics and tumor characteristics including extrahepatic metastases, tumor differentiation, and the percentage of liver involvement by the tumor. Prior to treatment, two of the patients in the chemotherapy only group died (20%); all patients in the RE group received treatment as randomized. All 21 patients were included in the intention-to-treat analysis. Eight patients in the RE group had a confirmed partial response; none of the chemotherapy only group had a partial response ($p < 0.001$). The time to disease progression was significantly longer in the RE group (18.6 versus 3.6 months, $p < 0.0005$).

Similarly, median overall survival was significantly longer in the RE group (29.4 versus 12.8 months, $p < 0.025$). Improvements in quality of life were similar in both groups ($p = 0.96$). Grade 3 and 4 toxicities were more common in the combined therapy group (13 versus 5, p not reported). Toxicities in the RE group included one patient who developed a liver abscess, a second patient who developed radiation-induced cirrhosis, and a third patient who developed recurrent neutropenia and died from sepsis.

Harms

There are a large number of publications in the literature describing the side effects and more significant adverse events associated with RE.^{12-14, 17, 67, 72-81} Patients commonly experience post-embolization symptoms including fever, nausea, vomiting, fatigue, anorexia and some abdominal pain. In the trials and case series reviewed for this assessment, between 20% and 55% of patients reported some of these symptoms. Pre-medication with corticosteroids followed by a steroid taper helps limit the inflammation thought to be partially responsible for these symptoms. Anti-emetics are routinely given with the procedure and on an as needed basis during one to two weeks following the procedure.

More serious radiation induced liver disease can lead to veno-occlusive disease, cirrhosis, and liver failure. One large case series, which included both primary and secondary liver tumors treated with RE, reported radiation induced liver disease in 4.1% of treated patients (28/680).⁷⁵ Older patients, smaller patients, those with pre-existing liver disease, and those requiring embolization of the entire liver are at highest risk of serious liver injury. Thoughtful patient selection and careful dosimetry limit the risk of this potentially life-threatening complication.

Radiation pneumonitis is a known complication of RE. Careful measurement of the lung shunt fraction and reducing the amount of microspheres injected if the shunt fraction is high can largely prevent this complication. Recent series suggest that the incidence of radiation pneumonitis should be less than 1%.¹²

Gastric and duodenal ulcerations are also potential complications related to shunting of blood carrying microspheres from the hepatic artery into the splanchnic circulation, usually through anatomic variants in the vasculature.^{72-74, 76, 79} Pretreatment angiography is essential both to identify arteries to avoid when planning the microsphere infusion and to embolize those arteries leading to the GI tract that cannot be avoided. GI tract ulcers may occur in as many as 5% of patients.^{74, 78, 82}

Finally, as with any transarterial catheter based therapy, there is always some risk of vascular injury, plaque emboli, and infection. Other reported complications include liver abscesses, lymphopenia, and biliary tree injury.^{67, 75, 78}

Summary

The three comparative studies all used different control interventions. The non-randomized study did not demonstrate any convincing improvements over chemoembolization. However, in both randomized trials, RE clearly had an impact on response rates and time to progression. In addition, compared with 5-fluoruracil and leucovorin, it appeared to improve overall mortality. However, there are several important concerns. First, the chemotherapy used as the control would not be considered the standard first line treatment and the response rates in the control arms (0% and 18%) were much lower than usually observed with chemotherapy. Recent clinical trials of first line systemic chemotherapy for inoperable liver metastases report 50% or higher response rates.⁸³ Furthermore, the trials were small and chance events may influence the findings. For instance, it is notable that 20% of patients in the control arm of the trial by Van Hazel et al died before receiving chemotherapy. The common toxicities were generally mild and the more serious grade 3 and 4 toxicities were relatively uncommon. Overall, the results suggest that there may be a role for RE, but the lack of a mortality benefit in the larger trial and the extremely small numbers in the second trial preclude definite conclusions.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

It is not straightforward to identify the appropriate alternative therapy with which to compare RE. In patients who have not received systemic chemotherapy to treat inoperable metastases to the liver, multi-agent chemotherapy based on oxaliplatin or irinotecan would be the appropriate comparator. In patients with tumors amenable to radiofrequency ablation, that may be an appropriate comparator. Finally, the appropriate treatment option for patients who have failed multiple rounds of systemic therapy. HAC and TACE are often tried, but as noted above, the most recent expert panel convened by the NCCN could not come to a consensus on the appropriate use of these therapies.⁶

There are currently at least two large trials (SIRFLOX and FOXFIRE) randomizing over 800 patients to first line chemotherapy with or without Yttrium microsphere radioembolization. Another trial is randomizing 250



patients to radiofrequency ablation, chemoembolization, or RE. There are also at least a dozen smaller trials evaluating RE with second or third line chemotherapy or in the setting of salvage therapy. The appropriate clinical trial data to guide patients and clinicians in deciding when to use RE in the treatment of inoperable liver metastases should be available in the next few years. Until the availability of additional data, TA criterion 4 is not met.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, clear improvements compared with standard surgery have not been demonstrated outside of the investigational setting. While RE has been performed in many centers for several years, TA criterion 4 must be met for TA criterion 5 to be considered met.

TA Criterion 5 is not met.

CONCLUSION

Colorectal cancer commonly metastasizes to the liver. Surgical resection of the liver tumors can be curative, but it is not always possible to perform the surgery and preserve a viable liver. The current standard of care is to use multi-agent systemic chemotherapy to treat inoperable liver metastases. External beam radiation therapy is rarely used because normal liver tissue is very sensitive to radiation. RE capitalizes on the differing blood supplies of normal liver tissue and liver tumors to deliver high dose radiation directly to the tumor while sparing most of the normal liver.

Twenty-two case series with data on patients with metastatic colorectal cancer have demonstrated that it is feasible to deliver radiation therapy to liver tumors and achieve at least partial remission in a substantial proportion of patients with relatively few serious adverse events. Procedure specific adverse events such as radiation pneumonitis, GI ulceration and radiation induced liver disease have been characterized and pretreatment planning strategies have been developed to limit their frequency and severity.



The results of the two randomized trials described above are encouraging, but not definitive. Both demonstrated improvements in disease-free survival and a trend towards longer overall survival. However, the trials were very small (less than 100 patients in total) and the response rates in the control groups were lower than expected. Furthermore, the control groups did not use the standard first-line therapy for colorectal cancer metastatic only to the liver. Ongoing clinical trials that are randomizing over 800 newly diagnosed patients to first line chemotherapy with or without RE should define the efficacy of combined therapy and the associated additional toxicity. Similarly, the data on the utility of RE as salvage therapy for patients who have failed multiple rounds of chemotherapy is limited and immature.

RECOMMENDATION

It is recommended that radioembolization for the treatment of inoperable liver metastases from colorectal cancer does not meet CTAF TA Criterion 2 through 5 for improvement in health outcomes.

February 17, 2010

This is the first review of this technology by the California Technology Assessment Forum

The California Technology Assessment Forum voted to accept the recommendation as written.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) has not conducted an assessment of this technology..

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a National Coverage Determination for this technology.

California Radiological Society (CRS)

A CRS representative will be in attendance at the meeting.

American Society of Therapeutic and Radiation Oncology (ASTRO)

An ASTRO representative provided testimony at the meeting on behalf of ASTRO, ACRO and the CRS.

Society for Interventional Radiology (SIR)

A SIR representative provided testimony at the meeting.

American College of Radiation Oncology (ACRO)

An ACRO representative will be in attendance at the meeting.

American Gastroenterological Association (AGA)

An AGA representative provided testimony at the meeting.

Association of Northern California Oncologists (ANCO)

ANCO was invited to provide an opinion regarding this technology and representation at the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC was invited to provide an opinion regarding this technology and representation at the meeting.

American Cancer Society (ACS)

The ACS does not have a specific recommendation or guidelines related to this cancer related topic. The absence of ACS comments reflects neither favorably or unfavorably on this procedure. A representative will not be attending the meeting.



ABBREVIATIONS

CTAF	California Technology Assessment Forum
HAC	Hepatic artery chemotherapy
TACE	Transarterial chemoembolization
RE	Radioembolization
NCCN	National Comprehensive Cancer Network
SIRT	Selective internal radiation therapy
GI	Gastrointestinal
FDA	Food and Drug Administration
PMA	Premarket Approval
IHAC	Intra-hepatic artery chemotherapy
HDE	Humanitarian Device Exemption
HCC	Hepatocellular carcinoma
DARE	Database of Abstracts of Reviews of Effects
NR	Not reported
RECIST	Response Evaluation Criteria on Solid Tumors

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