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Selective Internal Radiotherapy (SIRT) In the Management of Chemotherapy Refractory Cancers with Liver Predominant Metastasis: Results from a Tertiary Care Hospital in Western Australia

Muhammad A Khattak[1, 2, 3*], Jiuan Ting[4] and James Anderson[4]

[1] *Fiona Stanley Hospital, Perth, Western Australia, Australia*

[2] *University of Western Australia, Perth, Western Australia*

[3] *Edith Cowan University, Perth, Western Australia*

[4] *Royal PerthHospital, Perth, Western Australia, Australia*

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***Corresponding author:** *Muhammad Adnan Khattak, Department of Medical Oncology/University of Western Australia, Fiona Stanley Hospital, 11 Robin Warren Drive, Murdoch, Australia, Tel: +61 8 6152 2222; Fax: +61 8 6152 4080; E-mail: adnan.khattak@health.wa.gov.au*

Abstract

Aim: To retrospectively evaluate the efficacy and safety of Selective Internal Radiotherapy (SIRT) via 90Y microsphere radioembolisation as salvage therapy in patients with unresectable liver metastases from different tumour types, in a single tertiary centre.

Methods: We conducted a retrospective case-series analysis, with demographic and clinical information collected from departmental databases, Western Australia Cancer Registry, electronic medical records and medical case notes. The patients were divided into colorectal cancer (CRC) and non-CRC tumour groups.

Results: A total of 45 patients were treated between April 2006 and November 2014; 68.9% of patients (n=31) had CRC. Other tumour types included breast (n =4), hepatocellular carcinoma (n=3), carcinoid (n=3), cholangiocarcinoma (n=3) and squamous cell carcinoma (n=1). Thirty-seven patients were evaluable for response, and thirty-five were evaluable for toxicity. 9 patients had stable disease, and a further 15 demonstrated partial response following treatment. Median overall survival (OS) was 197 days, and median progression free survival (PFS) 90.5 days. The response rate and survival appeared to be better in the CRC group compared to the non-CRC group. Treatment related complication rate was low.

Conclusions: SIRT should be considered for the management of chemotherapy refractory cancers with liver predominant metastases.

Key words: Selective Internal Radiotherapy; Colorectal; Cancer

Introduction

The effective treatment of liver metastases continues to present a management challenge in patients with advanced malignancy. Complete surgical resection remains the best option for improved survival, however most patients are not suitable for surgery [1]. Despite advances in systemic treatment, liver metastases are commonly chemo-refractory [2]. Hence, targeted local-regional therapies are increasingly used. Radioembolisation with 90Y-microspheres or Selective Internal Radiotherapy (SIRT) is one such modality. It is increasingly used as salvage therapy for chemorefractory and unresectable liver metastases from colorectal cancer (CRC) and other tumour types.

The technical details of this procedure are well described elsewhere [3]. 90Y-labelled microspheres are injected via a temporary hepatic artery catheter, placed percutaneously through the brachial or femoral artery. The dose and activity of 90Y-labelled microspheres is adjusted according to tumour volume, lung shunting fraction, and patient body surface area. Analysis of the distribution of microspheres following SIRT treatment shows that liver metastases derive their blood supply almost exclusively from the hepatic artery, whilst the portal circulation supplies the normal liver parenchyma [4]. This enables the delivery of high dose radiation, selectively to liver metastases.

The results of previous studies using 90Y-microspheres as salvage treatment for liver metastases have been encouraging. Results from phase II/III prospective clinical trials and retrospective studies appear to show low toxicity, high tumoral response rates, and increased survival times for a substantial proportion of patients [5]. The majority of trials are in patients with metastatic CRC, receiving SIRT either alone or combined with chemotherapy. Radioembolisation appears to delay disease progression and prolong survival in patients with metastatic CRC, compared with randomized, matched-pair or historical controls [6]. Survival time for the use of SIRT alone in these cases ranges from 4.5 to 12.6 months [7]. There may be an additional benefit from receiving SIRT with concurrent chemotherapy [2]. Results in other tumour types may be less promising [8].

 ***Corresponding author email:** adnan.khattak@health.wa.gov.au*

Appropriate patient selection for SIRT is important. Consensus panel guidelines suggest cases should have liver-dominant tumour burden, minimal extrahepatic disease (EHD), adequate functional liver reserve, blood counts and renal function, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and a prognosis of >3 months [9]. Contraindications to therapy include a compromised portal vein, and prior radiotherapy to the liver. A standard pre-treatment imaging work-up includes mesenteric and hepatic CT angiography, and hepatic artery perfusion scintigraphy using 99m technetium-labeled macro aggregated albumin (MAA) [10]. This is used to delineate hepatic vasculature and anatomy, identify non-targeted flow and to quantify the degree of hepatopulmonary shunting, in order to identify patients at increased risk of GI or pulmonary toxicity from SIRT.

Previously published studies report typical side effects as being mild and self-limiting. A mild post-radiation syndrome, consisting of abdominal pain, fatigue, nausea and vomiting, anorexia, and fever occurs in 20-55% of patients [11]. GI ulceration has been reported in 4-10% of cases, usually developing 2-6 weeks post-procedure [11]. Radiation induced liver damage can occur in 4% of patients, manifesting between 4 weeks to several months after treatment [7]. Radiation pneumonitis and cholecystitis is rare.

The aim of this study was to retrospectively evaluate the efficacy and safety of SIRT via 90Y microsphere radioembolisation as salvage therapy in patients with unresectable liver metastases from different tumour types, in a single tertiary care centre in Western Australia.

Materials and Methods

We conducted a retrospective case-series analysis, in order to review toxicities and outcomes in patients receiving SIRT at a single tertiary center (Royal Perth Hospital, Western Australia). Data was retrospectively collected from the Department of Medical Oncology and Department of Nuclear Medicine databases, with supplementary information collected from the WA Cancer Registry, electronic medical records and medical case notes.

We identified a series of 45 patients receiving SIRT treatment for liver metastases from April 2006 to November 2014. All cases were referred by their medical oncologist, and discussed in a multidisciplinary setting, in order to determine suitability for the procedure. The pre-treatment assessment and SIRT procedure was performed consistent with standard practice. An experienced interventional radiologist performed each procedure. All patients were routinely followed up in Medical Oncology outpatient clinic. The patients were divided into CRC and non-CRC tumour groups, as well as being assessed as a whole.

Patient medical records were used to identify toxicities present at 2 weeks, 1 month and 3 months. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Staging investigations were reviewed to determine a response rate for each patient based on Response Evaluation Criteria in Solid Tumours (RECIST) guidelines [12]. A Partial Response (PR) was defined as ≥30% size reduction in the size of the liver lesion. Stable Disease (SD) was defined as between a <30% reduction or 20% increase in the size of the treated liver lesion. Progressive Disease (PD) was defined as a 20% increase in the size of tumours. The Objective Response Rate (ORR), (defined as the percentage of patients with a complete or partial response), and the Disease Control Rate (DCR), (defined as the sum of complete, partial and stable disease rates), were calculated as endpoints in the overall, CRC and non-CRC groups. The results of staging investigations and date of death were retrospectively analyzed to determine overall survival (OS) and progression free survival (PFS).

Results

A total of 45 patients underwent treatment between April 2006 and November 2014 (Table 1). There were 26 males and 19 females, with a median age of 58.0 (range 32-81). 86.4% of patients had an ECOG performance status of 0 or 1.

68.9% of patients (n=31) had CRC. Other tumour types included breast (n =4), HCC (n=3), carcinoid (n=3), cholangiocarcinoma (n=3) and SCC (n=1). 60% of patients had no extra-hepatic disease. 66.7% of patients had a hepatic tumour burden <50%. Comparison with the CRC group reveals that those with non-CRC had a lower median age, generally worse performance status, a greater proportion of female patients and had less concurrent chemotherapy.

84.4% of patients had failed prior systemic chemotherapy. 47.9% of patients received concurrent chemotherapy during SIRT. Generally, concurrent chemotherapy amongst the CRC patients was 5-FU based. A small number of patients had also received prior targeted loco-regional therapy for liver metastases, including SIRT (n=1), surgical resection (n=2), radiofrequency ablation (n=2), and transarterial chemo-embolisation (n=4).

Amongst these patients, a total of 48 procedures were performed. Two patients underwent SIRT therapy twice during the course of treatment. One patient had a failed procedure due to hepatic artery dissection before undergoing a successful procedure. 35 out of 45 patients had died at time of document review. 2 patients with CRC were lost to follow up.

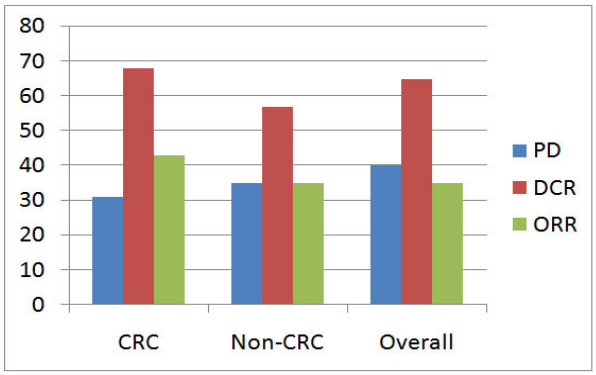
The response of 8 patients could not be assessed; this was due to the absence of appropriate scans (n=5), death within two months of procedure (n=2), and a failed SIRT procedure (n=1).

At a median follow up of 3months, 9 patients had stable disease, and a further 15 demonstrated a partial response (Figure 1). The majority of those patients with stable disease (n=8) or a partial response (n=9) had no extra-hepatic disease. There was no statistically significant difference between the CRC and non-CRC group.

Table 1: Patient Characteristics

	Overall (%)	CRC (%)	Non CRC (%)
Number of Patients	45	31 (68.9)	14 (31.1)
Number of Procedures	48	33 (68.8)	15 (31.3)
Age (median)	58	62	51.5
Male	26 (57.8)	22 (71)	4 (28.6)
Female	19 (42.2)	9 (29)	10 (71.4)
ECOG* 0	12 (26.7)	11 (35.5)	1 (7.1)
ECOG unknown	10 (22.2)	7 (22.6)	3 (21.4)
Extrahepatic disease present	16 (35.6)	10 (32.3)	6 (42.9)
Extrahepatic disease absent	27 (60)	19 (61.3)	8 (57.1)
Extrahepatic disease unknown	2 (4.4)	2 (9.7)	0
Prior systemic chemotherapy	38 (84.4)	27 (87.1)	11 (78.6)
Unknown previous systemic chemo	3 (6.7)	1 (3.2)	2 (14.3)
Prior local liver treatment (per procedure)	9 (18.8)	2 (6.1)	7 (46.7)
Unknown prior local liver treatment	4 (8.9)	4 (12.1)	0
Concurrent chemotherapy	23 (47.9)	19 (57.6)	4 (26.7)
Unknown chemotherapy	4 (8.3)	4 (12.1)	0
Hepatic tumour burden			
0-25%	18 (40)	15 (48.4)	3 (21.4)
26-50%	12 (26.7)	7 (22.6)	5 (35.7)
51-75%	11 (24.4)	6 (19.4)	5 (35.7)
76-100%	3 (6.7)	3 (9.7)	0

*Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status; CRC = Colorectal; Non-CRC: Non-Colorectal



*Abbreviations: ORR = Objective response rate, DCR = disease control rate, PD = progressive disease.

Figure 1: Response rates: Overall, CRC and non-CRC groups

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Median overall survival (OS) was 197 days for the whole group, and median progression free survival (PFS) 90.5 days (Table 2)

The majority of adverse events were mild and self-limiting, peaking at 2 weeks and settling by 3 months. A mild post radiation syndrome was common in the first 3 months; consisting primarily of abdominal pain (44.7%) followed by nausea (39.5%), lethargy (31.6%) and fever (18.4%) (Table 3). Toxicity data could not be collected for 10 patients due to inadequate documentation.

Serious adverse events (classed as grade 2+) occurred in 7 cases (18.4%); including gastric/duodenal ulceration, gastritis, and radiation induced liver disease (RILD), cholecystitis and colitis/pancreatitis (Table 4). Comparing the two groups, there was a higher rate of Grade 2+ complications in the non CRC group as opposed to the CRC group. Grade 2+ complications occurred in 5/12 (41.7%) procedures in the non CRC group as opposed to 4/26 (15.4%) procedures in the CRC group.

Table 2: Survival outcomes in CRC and non-CRC patient groups

	Median PFS (days)	Median OS (days)
CRC	133.5	237
Non CRC	62	169
Total	100	233

*Abbreviations: PFS = Progression Free Survival; OS = Overall Survival; CRC = Colorectal Cancer; Non CRC = non-colorectal

Table 3: Adverse Events

Adverse events	24h	>24h - 3 months	>3 months
Abdominal pain	4	17	4
Nausea and vomiting	1	15	4
Pneumonitis	0	0	0
Cholecystitis	0	1	0
Gastritis	0	2	2
Gastric/duodenal ulceration	0	1	2
Lethargy	0	12	5
RILD	0	2	0
Fever	0	7	0
Hepatic a. dissection	1	0	0
Haematoma	1	0	0
Colitis / pancreatitis	0	1	0

*Abbreviations: RILD = radiation induced liver disease. Severity classed according to CTCAE

Table 4: Serious Adverse Effects

	CRC	Non CRC
Gastric/duodenal ulceration	0	3
Gastritis	2	0
RILD	1	1
Cholecystitis	1	0
Colitis / pancreatitis	0	1

*Abbreviations: RILD = Radiation Induced Lung Disease; CRC = Colorectal; Non-CRC: Non-Colorectal

Discussion

This retrospective case-series adds to the published experience documenting efficacy and safety outcomes from the use of SIRT as salvage therapy for liver metastases in CRC and other tumour types.

A recent systematic review of twenty studies, comprising 979 patients with chemo-refractory CRC and liver metastases reported rates of complete response, partial response and stable disease were 0 (range 0-6), 31 (range 0-73), and 40.5 (range 17-78) percent, respectively [13]. The median progression free survival was 4.9 months and the median overall survival was 12 months [13]. Elsewhere, median overall survival following SIRT as salvage therapy for liver metastases has been reported to range from 4.5 to 12.6 months for CRC and other primary cancers [5]. Our CRC group had response rates consistent with those reported in this systematic review. They demonstrated a similar median progression free survival (4.5 months), and a slightly lower median overall survival (7.9 months).

The data on the use of SIRT as salvage therapy in non-CRC patients is less robust. One retrospective cohort study by Bester et al, evaluated outcomes amongst patients with CRC (n=224) and non-CRC (n =115) [5]. Overall survival was similar between the groups (11.9mo and 127mo, respectively), suggesting that the efficacy of radioembolisation might be independent of tumour origin. Our data revealed survival was worse in the non-CRC group compared to the CRC group.

Our toxicity and safety data was consistent with published literature, demonstrating an acceptable safety profile for the use of SIRT in this setting. Acute toxicity is reported in 11-100% (median 41%) of cases, most of which is mild (grade 1 or 2) [11]. 44.7% of our patients reported features of a mild post-radiation syndrome. Mild adverse effects were generally well controlled and did not persist beyond 3 months. Consistent with prior experience, serious complications such as ulceration and RILD were uncommon. It appeared that the rate of adverse effects was higher amongst our non-CRC tumour group.

Our study appeared to show lower response rates and increased toxicity amongst the non-CRC group compared to CRC group. This could be explained by clinco-pathological differences between groups, such as the extent of tumour hepatic burden, extra hepatic disease, concurrent chemotherapy, varying ECOG performance status and complication rates. However, it is difficult to interpret due to the small sample size of our study, and the limitations of missing data from our retrospective analysis. Current published literature is inconsistent on this issue, and further studies are required.

Regardless of the origin of metastatic lesions, there is widespread evidence to show that outcomes for the majority of patients with unresectable, chemorefractory disease are poor [14, 15]. It is difficult to find a true comparator group for our patient population. However, a median survival of less than 6 months has been reported in the literature for patients with metastatic CRC refractory to standard chemotherapy [16]. In light of this poor prognosis, SIRT appears to be a valuable salvage therapy, with an acceptable toxicity profile.

Radioembolisation with 90Y-microspheres is a feasible option as salvage therapy in patients with unresectable, chemorefractory liver metastases from colorectal and other primary tumours. Our study contributes to the current body of research, showing improved overall survival and progression free survival overall after treatment with SIRT. The treatment may be less effective in the non-CRC group compared to the CRC group. Common side effects are mild and self-limiting, and serious side effects are very rare. SIRT is gaining increasing recognition as a valuable treatment modality, with an acceptable safety profile, which can improve survival outcomes in poor prognosis tumours with few other treatment options.

Conclusion

SIRT should be considered as a potential liver targeted treatment option in patients with chemo-refractory liver limited disease from advanced CRC. There is emerging data regarding its utility in other tumour types like hepatocellular carcinoma as well as in the first line management of CRC with liver disease. Although SIRT has an acceptable safety profile, it should be done in experienced centres with expertise available to manage any potential complications.

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