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ORIGINAL ARTICLE

Predictors of response to radio-embolization (TheraSphere®) treatment of neuroendocrine liver metastasis

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Abstract

Background: Neuroendocrine tumours (NET) frequently metastasize to the liver. NET liver metastasis has been shown to respond to Yttrium-90 microspheres therapy. The aims of the present study were to define factors that predict the response to radio-embolization in patients with NET liver metastases.

Methods: From January 2006 until March 2009, all patients with NET liver metastasis that received radio-embolization using TheraSphere® (glass microspheres) were reviewed. The response was determined by a change in the percentage of necrosis (ΔN%) after the first radio-embolization based on the modified RECIST criteria (mRECIST) criteria. The following confounding variables were measured: age, gender, size of the lesions, liver involvement, World Health Organization (WHO) classification, the presence of extra-hepatic metastasis, octereotide treatment and previous operative [surgery and (RFA)] and non-operative treatments (chemo-embolization and bland-embolization).

Results: In all, 25 patients were identified, with a median follow-up of 21.7 months. The median age was 64.6 years, 28% had extra-hepatic metastasis and 56% were WHO stage 2. Post-treatment, the mean ΔN% was 48.4%. Previous surgical therapy was a significant predictor of the response with a response rate of 66.7 ΔN% vs. 31.5 ΔN% ($P = 0.02$). Bilateral liver disease, a high percentage of liver involvement and large metastatic lesions were inversely related to the degree of tumour response although did not reach statistical significance.

Conclusion: Radio-embolization increased the necrosis of NET liver metastasis mainly in patients with less bulky disease. This may imply that surgical therapy before radio-embolization would increase the response rates.

Keywords

liver, non-colorectal metastases < liver, radiological intervention – fluoroscopically guided < liver

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Background

Neuroendocrine tumours (NET), formerly categorized into carcinoids and pancreatic islet tumours, represent a heterogeneous group of slow growing tumours that originate from the same cell line and have the potential to secret hormones. Although commonly of a gastroenteropancreatic origin, they can originate from any neuroendocrine cell in the body. The overall incidence rate is reported to be 5.25 per 100 000 people.[1] An increase in the incidence of the disease is noted, which is partly attributed to the rising awareness and improved diagnostic strategies.[2,3]

In spite of the improvements in the recognition and treatment of primary NET over the past decades, distant metastasis at the time of diagnosis is reported in 13% of cases.[1,3] The most frequent site of distant metastasis is the liver.[1] In fact, NET metastases represent 10% of all metastatic liver lesions.[4] These metastatic

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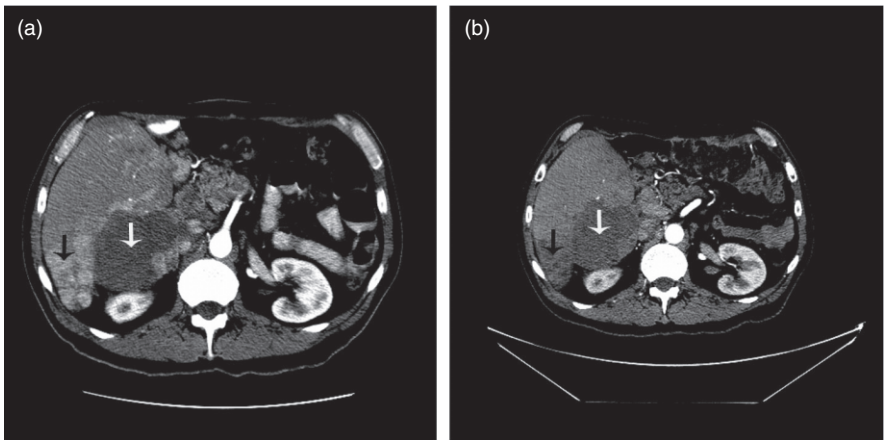

Figure 1 Therasphere therapy after surgical intervention. (a) An abdominal computed tomography (CT) scan showing a previously-treated neuroendocrine tumour (NET) metastatic lesion with radiofrequency ablation (RFA) in segment VII (white arrow) with no enhancement. However, multiple enhancing metastatic nodules (black arrow) are present adjacent to the ablated segment. (b) CT scan images of the same patient 3 months after ^{90}Y therapy of the right lobe of the liver showing a complete response. The vascular enhancement has virtually disappeared, but the lesions themselves are persistent

lesions will subsequently be responsible for the more alerting and disabling symptoms. Those are caused by a pressure effect on adjacent structures, liver parenchymal replacement and/or carcinoid syndrome as a consequence of excess hormonal secretion.[5] Surgical therapy offers the best chance of curing localized NET liver metastasis, with a 5-year survival rate of approximately 75%.[6–8] Unfortunately, in the majority of patients the disease progresses beyond this therapeutic window, leading to a 5-year survival rate of less than 20%.[6–8]

Patients with metastatic disease are treated based on the assessment of symptoms, performance status, tumour differentiation, burden of the disease and progression rate.[3] Multiple treatment modalities have been implied and studied with variable results. These include: surgery, biotherapy, chemotherapy, chemo-embolization and radio-embolization, also called selective internal radiation therapy (SIRT). The main goals of treatment are relieving symptoms, improving the quality of life and, if possible, prolonging survival. The relatively low disease incidence and the diversity in its presentation, has led to the lack of well-conducted randomized controlled trials comparing the efficacy of different treatment options.

Radio-embolization using yttrium-90 (^{90}Y) microspheres has been proven to be effective in the treatment of NET liver metastases.[9–11] TheraSphere® is the material used to deliver the ^{90}Y radio-embolization in our centre, which is a glass-based microsphere. The ^{90}Y radio-embolization is considered an expensive and not readily available line of therapy that when associated with a significant response may have a potential survival benefit.[12] Hence the increasing needs to define factors that predict a better response to this therapy. This will also help in achieving the maximum benefit of the available treatment modalities.

The aims of the present study were to define factors that can predict a better response in patients receiving ^{90}Y radio-embolization as a treatment for NET liver metastases.

Method

From January 2006 until March 2009, a total of 25 patients were identified using the McGill University Health Centre NET database. These patients were diagnosed with NET liver metastasis and received ^{90}Y therapy using TheraSphere® in the course of their management.

The 'McGill University Health Centre NET tumour board' dictates all treatment plans for those patients. The board includes members of Hepato-pancreato-biliary surgery, interventional radiology, nuclear medicine and endo-medical oncology. The overall strategy is based on an aggressive surgical approach with the aim to remove most (if not all) of the tumour burden in patients with limited disease. Other treatment modalities were considered when operative techniques were not applicable. ^{90}Y radio-embolization was reserved for patients with advanced (multifocal) disease within the liver and those who progressed or had disease recurrence after surgical therapy (Fig. 1). All patients with well-differentiated tumours are on long-acting octeriotide treatment.[13] Patients with abnormal liver function [international normalized ratio (INR) > 1.5 IU, bilirubin > 60 mmol/l], and those who had previous external beam radiation were not offered the ^{90}Y treatment. Furthermore, two patients were offered the ^{90}Y treatment but did not receive it because of a hepatopulmonary shunt (>20%) and hence, were excluded from the present study.

Before treatment, baseline imaging was performed which consisted of a tri-phasic computed tomography (CT) of the chest and abdomen and an octreotide scan. A ^{18}fluoro-deoxyglucose

positron emission tomography (FDG-PET) scan was done for seven patients who were seen more recently. The aims of these studies are to measure tumour size, the percentage of hepatic involvement and the extent of extra-hepatic disease. Afterwards, three planning studies were performed. These were a dedicated arterial angiography, a shunt study and volume CT acquisition. The goal of the angiogram was to identify and embolize any potential sources of non-target embolization to intestinal organs, such as a right gastric artery, or the gastro-duodenal. Any at risk vessels were embolized in the same session. With the angiographic catheter in place, the patient was transferred to the Nuclear Medicine department for the shunt study. This consists of injecting Technetium-99 m labelled macro-aggregated albumin (MAA) particles into the hepatic artery and monitoring to determine the fraction shunted to the lungs. Finally, a dedicated CT scan was performed with a direct contrast injection in the hepatic artery to identify the lobe or segment being treated and allow precise volume measurements. The correct dosing of ^{90}Y to be administered was calculated using the standard formula described by the supplier. The inputs for this are the volume of the targeted area of the liver, including normal and tumour tissue, the target radiation dose measured in gray (Gy) and the percentage of the shunt fraction. As all of these patients had normal underlying liver function, the target does range was 140 to 150 Gy.[14]

After angiographic confirmation, the ^{90}Y microspheres are delivered via the target artery using a selective, lobar or bi-segmental, approach depending on the location of the NET metastases. The patients were monitored for a few hours after therapy to ensure the absence of acute complications. Patients were regularly followed up afterward. This consists of clinical assessment, a liver function test, a CT scan and a nuclear scan at 3–4 weeks after the treatment and every 3–6 months thereafter. During which, visualization of the treatment response and observation for late complications is addressed. The treatment response was assessed by measuring the percentile difference in tumour necrosis (ΔN%) before and after the treatment rather than the change in tumour diameter. This is done using the modified RECIST criteria (mRECIST), which is the recommended method in measuring the tumour response to embolic therapies.[15] According to this criterion, the response of target lesions was classified into four categories. A response is said to be 'complete' when the entire intra-tumoural arterial enhancement disappears. A 'partial response' is defined as having at least a 30% decrease in the sum diameter of the enhancing portion of the target lesions in reference to the baseline sum of diameters. A 'progressive disease' is an increase of at least 20% in the sum of the target lesions in reference to the baseline. Any case that does not qualify for either a partial response or progressive disease is classified as 'stable disease'.[15]

Descriptive statistics are presented in the form of medians and percentages summarizing the following variables: age, gender, size (<2, 2–4 and >4 cm), liver involvement (<33%, 33–66% and >66%), WHO classification, the presence of extra-hepatic metastasis, octereotide treatment and previous operative (surgery and RFA) and non-operative treatments (chemo-embolization and bland-embolization). Independent-samples *t*-test, the paired *t*-test and Pearson's correlation coefficient were used to study the significance of a response. Analysis of covariance (ANCOVA) was used to adjust for possible confounders. Overall survival is presented using the Kaplan–Meier survival method. The objective is to study the effect of these defined variables on the rate of the tumour response (ΔN%) to ^{90}Y treatment.

Results

A total of 25 patients were enrolled in the study (16 males and 9 females); summarized in Table 1. Their median age was 64.6 years (range 34.6–90.4) and the median follow-up was 21.7 months (range 3.9–44.2) starting when patients had their first radio-embolization treatment. Most tumours are metastasis from a pancreatic primary (n = 13). Others originate from the small intestines (n = 6), lungs (n = 2), colon (n = 1) and of an unknown origin (n = 3). Diagnosis was based on the radiological appearance and a confirmatory histopathological examination in all cases. However, not all pathology reports had sufficient data to conclude an accurate WHO staging (Table 1).

All patients had TNM stage IV metastatic NET to the liver. The maximum diameter of the largest liver lesion was less than 2 cm in four patients, between 2–4 cm in 14 patients and more than 4 cm in seven patients. Lesions were confined to one liver lobe in eight patients, while involving both lobes in 17 patients. Radiological measurement of the tumour bulk was calculated against the total liver volume by an expert radiologist and expressed as the percentage of liver involvement. Based on this, patients were stratified into three categories; 11 patients had 33% or less involvement, five patients had between 33% and 66% involvement and nine patients had more than 66% liver involvement. Extra-hepatic metastases were discovered in seven patients at the time of diagnosis. Pathology review revealed 13 patients (52%) with well-differentiated NET (Table 2).

A total of 43 treatment sessions using ^{90}Y radio-embolization were performed. Eleven patients had a total of two sessions, two patients had three sessions and one patient had four sessions. The mean radiation dose per treatment was 141.1 Gy (range = 90–159). In general, treatment sessions were planned so that patients received no more than one dose of ^{90}Y in the target liver volume. Two patients did undergo re-treatment in the same area at an interval of about 1 year, these patients had responded initially, but then progressed. No patients received three or more treatments in the same target volume. The average time interval from diagnosis to the first ^{90}Y was 53 months. The overall difference in necrosis observed after ^{90}Y treatment is 48.4 ΔN% which is highly significant ($P < 0.001$). Before radio-embolization, 20 patients (80%) were on octeriotide treatment, 12 patients (48%) underwent a total of 16 operative treatments (eight liver resections and eight radio-frequency ablations) and six patients (24%)

Table 1 Baseline characteristics

Patients details (total = 25)	
Gender	
Male (*n*)	9 (36%)
Female (*n*)	16 (64%)
Age (years) (median)	64.6 (56.9–69.12)
Follow-up (months) (median)	21.7 (13.8–35.7)
Tumour characteristics	
Origin	*n* (percentage)
Pancreas	13 (52%)
Small intestine	6 (24%)
Lung	2 (8%)
Colon	1 (4%)
Unknown	3 (12%)
WHO	*n* (percentage)
Stage 2	14 (56%)
Stage 3	3 (12%)
Missing	8 (32%)
Differentiation	*n* (percentage)
Moderately/undifferentiated	14 (56%)
Well differentiated	3 (12%)
Missing	8 (32%)
Extra-hepatic metastases	*n* (percentage)
Yes	7 (28%)
No	18 (72%)
Liver involvement	*n* (percentage)
<33%	11 (44%)
33–66%	5 (20%)
>66%	9 (36%)
Liver lobes involved	*n* (percentage)
Unilateral	8 (32%)
Bilateral	17 (68%)
Maximum diameter of liver lesions	*n* (percentage)
<2 cm	5 (20%)
2–4 cm	10 (40%)
>4 cm	10 (40%)
Treatment details	
Before yttrium treatment	*n* (percentage)
Octeriotide	20 (80%)
Non-operative modalities	d6 (24%)
Operative modalities	12 (48%)
Number of yttrium sessions	*n* (percentage)
1 session	12 (48%)
2 sessions	10 (40%)
3 sessions	2 (8%)
4 sessions	1 (4%)

Table 2 A summary of tumour response rates (ΔN%)

Factor	***n***	**Tumour response rates (ΔN%)**
Previous operative treatment (surgery or radio-frequency ablation)		
Yes	12	66.6 %
No	13	31.5 %
		P-value = 0.02*
Liver lobes involved		
Unilateral	9	66.3 %
Bilateral	16	40.0 %
		P-value = 0.11
Extent of liver involvement		
≤66%	16	53.2 %
>66%	9	40.0 %
		P-value = 0.43
Maximum diameter of liver lesions		
≤4 cm	15	52.0 %
>4 cm	100	43.0%
		P-value = 0.58
Previous non-operative treatment (chemo-embolization or bland-embolization)		
Yes	6	51.7 %
No	197	47.7 %
		P-value = 0.82
Octeriotide treatment		
Yes	20	48.0 %
No	5	50.0 %
		P-value = 0.92

*Statistical significance was retained after adjusting for possible confounders; namely, liver lobes involved, extent of liver involvement and maximum diameter of liver lesions ($P = 0.041$).

underwent a total of seven non-operative treatments (five bland-embolization and two arterial embolization).

Although no immediate complications were reported, seven patients had grade 1–2 toxicities in the following 30 days. These complications included mild abdominal pain, itching, generalized fatigue, a low grade fever, weight loss and nausea and vomiting. Two other patients suffered grade 3–4 toxicities. One patient had abdominal pain that necessitated re-admission for pain control and the other had evidence of portal vein thrombosis on radiological studies. One patient died within 4 months as a result of a bleeding perforated duodenal ulcer thought to be caused by escaped beads. During the follow-up period, 12 out of the 25 patients died.

The mean ΔN% was 48.4% ± 38.7. Fifteen patients (63%) had at minimum a partial response to therapy based on the mRECIST criteria by having >30% ΔN%. Patients who had a previous operative intervention had a higher response rate of 66.7 ΔN% vs. 31.5

ΔN% ($P = 0.02$). Moreover, liver involvement of less than 66%, unilateral liver involvement and smaller metastatic lesions tended to have a higher response rate but this did not reach statistical significance; Table 2. There was no apparent linear correlation between radiation dose, per targeted liver volume, and the percentile difference in tumour necrosis ($r = 0.16$).

Patients who underwent surgical treatment tended to have unilobar disease (58%), with no more than 66% of liver involvement (83%) and a maximum tumour diameter of less than 4 cm (67%). Although formal multivariant analysis was not performed due to sample size limitation, analysis of covariance was attempted to control for possible confounders. After adjusting for liver lobes involved, the extent of liver involvement and the maximum tumour diameter, previous operative intervention remained a statistically significant predictor of a higher response rate (P 0.041).

Discussion

The 'silent' nature of NET progression draws attention towards exploring the best way to manage its spread. Around one in every seven patients has apparent metastatic disease at the time of diagnosis.[16] Moreover, 25–90% of patients are expected to develop metastases during the course of the disease; the liver being mostly involved.[16] Multiple treatment options are currently available and are constantly being explored with the aim for better outcomes. Surgery has been known to be the best option for resectable tumours. Unfortunately, NET liver metastasis are commonly multiple, small and scattered in nature.[17,18] Other options such as bland-embolization, chemo-embolization, somatostatin analogues, systemic chemotherapy and radiotherapy have been used with little to no survival benefit.[19–22] The current management of NET liver metastasis requires the use of these different treatments interchangeably. One of the emerging treatment modalities is radio-embolization using radioactive ^{90}Y microspheres. It is a modality that carries a promise of a safe and effective option as proven by multiple trials.[10,11]

TheraSphere® is a material used to deliver the ^{90}Y radio-embolization. It consists of ^{90}Y-embedded glass microspheres that are pure β-emitters (high energy) with a half-life of 64.2 h. The emitted radiation exhibits a mean tissue penetration of 2.5 mm and a maximum of 11 mm. These microspheres deliver a high dose of radiation to the intended malignant cells. There is a minimal ischaemic effect on the normal liver tissue, as the size and number of infused particles and the hypervascular nature of NET liver metastasis. Therefore, associated toxicities are more tolerable when compared with other embolic-based treatment options.[23–25] On the other hand, it has its share of drawbacks. Planning a radio-embolization consumes a lot of hospital resources; CT scans, angiographic liver mapping and +/– shunt embolization are of the minimal basic requirements. Furthermore, the microspheres are expensive and require an experienced interventional radiologist to perform the treatment. Hence, identifying the predictors of a response is an important step towards maximizing the benefit of ^{90}Y radio-embolization use.

In concordance with recent studies, our data shows a better response to ^{90}Y radio-embolization treatment in patients with less bulky NET liver metastasis. An aggressive surgical approach to debulk the tumour showed a significant improvement in response rates. In addition, the tumour burden (measured by percentage of liver involvement, the diameter of the lesions and the spread to both liver lobes) was inversely related to the amount of tumour necrosis in response to ^{90}Y treatment. These results suggest that debulking procedures, such as surgery and RFA, have an essential role in reducing the tumour burden, allowing the ^{90}Y treatment to achieve higher response rates.

A phase II trial by Sexena A *et al*. also looked at factors predicting response and survival after ^{90}Y radio-embolization for unresectable NET liver metastases.[26] Although measurement of the response was based on a change in actual tumour diameter rather than necrosis, three factors associated with a better response were identified. Those were female gender, a well-differentiated tumour and low hepatic tumour burden, in addition a longer survival was seen in patients with a better response.[26] Our data validates further the importance of tumour burden as a predictor of response to ^{90}Y radio-embolization treatment. A tumour involving more than 66% of the liver had a response rate of 40 ΔN% vs. 53.1 ΔN% in patients with less than 66% involvement. Bilobar disease was associated with a lower response (39.4 ΔN%) vs. unilobar disease (64.4 ΔN%). It is noted that previous surgical debulking was not associated with a better response to the treatment in the previous study by Sexena *et al*. In comparison, the present study shows a statistically significant higher response rate; 66.7 ΔN% vs. 31.5 ΔN% (P 0.02) in patients who had prior surgical treatment. Other studies, however, demonstrated the beneficial rule of surgical intervention in patients with metastatic NET to the liver.[16,27] Their data have suggested a better survival in patients undergoing an early surgical reduction of tumour load. Also, curative surgical intent showed better survival outcomes compared with palliative intent.

Several studies have looked at possible outcome predictors in patients with metastatic NET, verifying the prognostic values of TNM staging system as well as the WHO classification.[28–31] Other variables have also been identified as potential confounders. Most of these are related to the tumor's biology, bulk and extent of spread.[31,32] A review of 118 patients by Cosimo D *et al*. suggested that young age, a low number of liver metastasis, surgical treatment of primary and metastatic disease, as well as a slow tumour progression slope to be favourable prognostic factors.[33] The present study was not intended to examine the effect of ^{90}Y treatment on survival. Nevertheless, the overall median survival from the time of ^{90}Y treatment was 35.27 months which is slightly higher than previously published studies (Fig. 2).[12] In respect to the small number of patients studied in this review, no significant difference in survival could be attributed to any of the favourable predictors.

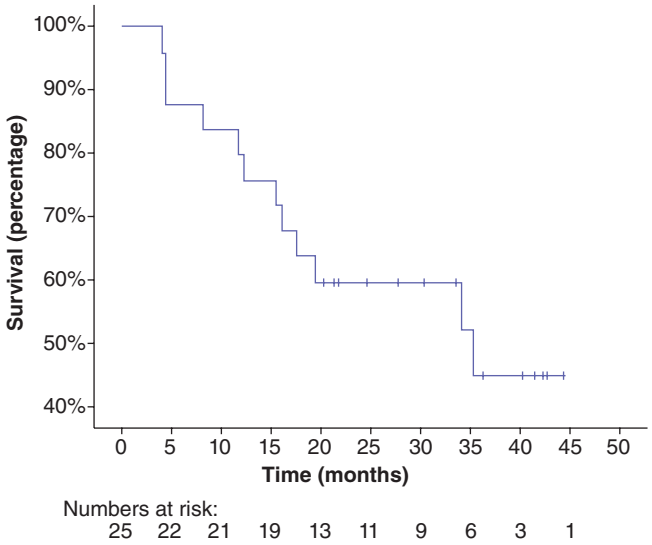

Figure 2 Overall survival

The expanding literature is in support of the use of cytoreductive strategies in patients with metastatic NET in terms of symptom control and overall survival.[16,22,26,33–35] Detecting survival advantage in patients with advanced NET disease that would require ^{90}Y treatment is not easy to conduct. The complexity and the heterogeneity of the patients in addition to the rarity of the disease are the main reasons. The present study, however, is focused to determine factors predicting the tumour response to ^{90}Y treatment. We believe that a collaborative multi-centric, randomized trial is needed to clarify the benefits of the cytoreductive strategies when combined with ^{90}Y treatment.

Conclusion

Radio-embolization increased the necrosis of NET liver metastasis. The benefit is greater in patients with less bulky disease. This implies that surgical treatment (resection or RFA) before radio-embolization would allow ^{90}Y treatment to achieve higher rates of response. The noted difference in the percentage of tumour necrosis was doubled in patients who had surgical treatment before the ^{90}Y radio-embolization. This effect might be attributed to the differences in the total radiation delivered to the smaller tumour burden. These data warrant a larger, prospective study with radio-embolization.

Conflicts of interest

None declared.

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