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Selective internal radiation therapy for neuroendocrine liver metastases

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1. Introduction

Selective internal radiation therapy (SIRT) with yttrium-90 (^{90}Y) microspheres is a promising treatment option for unresectable neuroendocrine tumour liver metastases (NETLM). Liver metastases, which present in 46–93% of patients at time of diagnosis depending of origin of the primary tumour, are a cause of significant mortality and morbidity. For this reason, patients with NETLM require optimal clinical management, using the combined skills of a multidisciplinary team.

The options available can be categorised as follows:

- Surgical, with or without ablation, e.g. RFA
- Medical, e.g. somatostatin analogues and/or chemotherapy
- Nuclear medicine, e.g. Peptide Receptor Radionuclide Therapy (PRRT)

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- Liver-directed therapies, e.g.
 - (a) Transcatheter Arterial bland Embolisation (TAE),
 - (b) Transcatheter Arterial Chemoembolisation (TACE)
 - Conventional TACE
 - Drug eluting beads (DEB)
 - (c) Selective Internal Radiation Therapy (SIRT) with ^{90}Y microspheres

2. Treatment approaches

The treatment approach to NETLM is dictated by the pattern of disease within the liver and beyond.

2.1. Liver metastases without extra-hepatic spread

Morphologically, there are three different patterns of liver metastases:

- (A) Simple Pattern: The metastases are confined to one liver lobe or limited to two adjacent segments. This “simple pattern” occurs in 20–25% of patients and is generally amenable to either:
 - (a) Surgery – minor or anatomical resection with or without ablation, e.g. RFA, OR

Table 1 – Summary of the clinical literature on SIRT in NETLM

Investigator	n	Therapy	ORR	SD	Symp.	PFS	Median survival
Kennedy ²	148 ^a	SIR-Spheres ^b	63.2%	22.7%		nr	70 mo
King ³	34	SIR-Spheres ^b + 5-FU	50%	14.7%	55%	nr	59% at 35.2 mo
Saxena ⁴	48	SIR-Spheres ^b	54%	23%	nr	nr	35 mo
Cao ⁵	58 ^a	SIR-Spheres ^b + 5-FU	39.2%	27.4%	nr	nr	36 mo
Jahangir ⁶	73 ^a	SIR-Spheres ^b	nr	nr	nr	10.6 mo	55.2 mo
Rhee ⁷	42	⁹⁰ Y microspheres	[92–94%] ^c		nr	nr	22 ^d & 28 ^b mo
Meranze ⁸	10	SIR-Spheres ^b	40%	60%	nr	nr	70% at 28 mo
Jakobs ⁹	25 ^a	SIR-Spheres ^b	20.8%	75%	92%	nr	96% at 12 mo
McGrath ¹⁰	26 ^a	SIR-Spheres ^b	58.3% ^e	33% ^e	2 of 3	nr	69.1% at 17 mo
Kennedy ¹¹	18 ^a	SIR-Spheres ^b	89% ^e	nr	nr	nr	89% at 27 mo
Coldwell ¹²	84 ^a	⁹⁰ Y microspheres	67%	33%	80%	nr	nr
Kalinowski ¹	9	SIR-Spheres ^b	67%	33%	↑ QoL	11 mo	57% at 36 mo
Murthy ¹³	8 ^a	SIR-Spheres ^b	12.5%	50%	nr	nr	14 mo
Paprottka ¹⁴	42 ^a	SIR-Spheres ^b	22.5%	75%	94.7%	nr	95% at 16.2 mo

mo: months; nr: not reported; Symp: symptomatic response.
^a Retrospective data. ^b ⁹⁰Y resin microspheres. ^c ORR + SD. ^d ⁹⁰Y glass microspheres. ^e Imaging + CgA.

- (b) Liver-directed therapy if the patient is not fit for surgery.
- (B) Complex Pattern: One major lesion but with smaller satellite lesions contra-laterally. This “complex bilobar pattern” occurs in 10–15% of the cases. Patients are treated with either:
- (a) Surgery – major one-step or two-step resection/ablation, OR
- (b) Liver-directed therapy if patients are not fit for surgery.
- (C) Diffuse Pattern: There are diffuse, multifocal liver metastases. This “diffuse pattern” occurs in 60–70% of the cases. Patients with this pattern of disease are unresectable and are generally treated with liver-directed therapy.

2.2. Liver metastases with extra-hepatic spread

Inoperable NETLM with extra-hepatic spread should initially be treated using non-surgical methods (e.g. biotherapy, chemotherapy, PRRT etc.) regardless of the extent of liver disease, and may be combined with liver-directed therapy such as SIRT, as appropriate. Surgical debulking may also be undertaken for selected candidates.

3. SIRT

The following conclusions can be drawn from the literature on SIRT in NETLM (see Table 1):

- Sufficient evidence exists to support the safety and effectiveness of SIRT for unresectable NETLM.

- Statistical significance was achieved when determining overall survival, suggesting that locoregional control of NETLM with SIRT may be of paramount importance for overall survival.
- The incidence of adverse events with SIRT is low, without evidence of treatment-related grade 4 events or radiation-induced liver disease (RILD).
- Overall survival was related to: the extent of tumour involvement, the presence of extrahepatic disease at the time of SIRT, good radiological tumour response (CR+PR), and histological grade of the tumour.

4. Conclusions

SIRT with ⁹⁰Y microspheres is a promising treatment option for unresectable NETLM. Patients with low hepatic tumour burden, well-differentiated tumour and no extrahepatic disease are the best candidates for SIRT.

Conflict of interest statement

The author has received research funding and has received honoraria from SIRTEX MEDICAL Australia and COVIDIEN Australia.

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