Is There a Role for Radiation in Neuroendocrine Neoplasms with Hepatic Metastases?

[1]Rebecca Zener, [2]Michael Lock, [3]Walter Kocha, [1]Robert Reid, [4]Douglas Quan, [4]Daryl Gray
[1]Departments of Medical Imaging, [2]Radiation Oncology and Physics, [3]Medical Oncology, [4]General Surgery,
London Regional Cancer Program, London Health Sciences Centre, and Western University, London, Ontario

ABSTRACT

Background: The liver is the most common metastatic site for neuroendocrine neoplasms (NEN). Its presence is a major prognostic factor. While stereotactic body radiotherapy (SBRT) has been successful in treating non-neuroendocrine hepatic metastases, it has not been incorporated into NEN hepatic metastases management. This study investigates radiation's potential role in treating NEN hepatic metastases.

Methods: Four patients with hepatic metastases from advanced gastrointestinal NEN were prospectively identified and treated with SBRT. Radiation treatment method consisted of respiratory-gated simulation and treatment, individualized dosing with radiobiological calculation of normal tissue complication probability.

Results: One patient with hepatic metastases from a gallbladder primary was only able to receive low-dose radiation (3000 cGy/10). She died of in-field recurrence 5 months post-SBRT. Two patients, one with hepatic metastases from a functional, well-differentiated, 5-HIAA positive, neuroendocrine small bowel carcinoma, and another with hepatic metastases from a well-differentiated, non-functional, pancreatic neuroendocrine carcinoma achieved progression-free, stable disease after being treated with 4200 cGy/6, and 5574 cGy/6 of SBRT, respectively. Both remain alive 3.5 years post-SBRT. The fourth patient was treated with SBRT for hepatic metastases from esophageal NEN without major toxicity, and remains alive more than 2 years post-SBRT. However, status of his disease and local control are unknown, as he has declined imaging follow-up. No NCIC CTC grade $\geq$2 toxicities were observed.

Conclusion: External beam radiation for NEN liver metastases appears to be well tolerated, and may achieve disease stability for a substantial period of time. While it is a small case series with a heterogeneous patient group, this represents the first case series of SBRT for NEN hepatic metastases, and the results are encouraging. The effectiveness of SBRT for NEN hepatic metastases, progression-free survival, control of tumor functionality, and determination of selection criteria warrants further investigation.

BACKGROUND

- Over 25% of patients with NEN have distant metastases at presentation. Liver is the most common location.
- Presence and distribution of hepatic metastases are major factors in prognosis and survival.
- Radiation-induced liver disease (RILD) has been a significant dose-limiting toxicity for liver radiation.
- SBRT has permitted dose escalated and precise conformal radiation delivery with increased local control and decreased liver-related toxicities in non-neuroendocrine liver metastases (eg. colorectal)
- SBRT has not been addressed in NEN hepatic metastases management.
- This case series is a preliminary investigation of radiation's potential role in treating gastroentero-pancreatic (GEP) NEN hepatic metastases.

METHODS

- Four patients with liver metastases from advanced gastrointestinal NEN were prospectively assessed.

- The radiation treatment method involved respiratory-gated simulation and treatment, individualized dosing with radiobiological calculation of normal tissue complication probability described separately[2].

- Imaging follow-up was performed at 1-, 3-, 6-, 12-, 18- and 24-months post-SBRT. RECIST criteria were used to assess tumor response.

RESULTS

Table I – Patient demographics

Case	Age at SBRT	Primary Tumor	# of hepatic metastases	Extra-hepatic disease	Pre-SBRT management
1	83 F	Gallbladder	2	-	Partial hepatectomy, cholecystectomy
2	39 M	Small bowel	3	+	Combined radioisotope chemotherapy, HACE, octreotide
3	61 F	Tail of pancreas	6	-	Distal pancreatectomy, splenectomy, partial hepatectomy, HACE, chemotherapy, Octreotide
4	76 M	Esophagus	1	-	Distal esophagectomy with gastric pull-up, chemotherapy

Table II – Summary of case primary tumour location, SBRT dose and outcomes

Case	Biologically equivalent dose (BED) in 2 Gy/Fraction	Dose (cGy) /fractions	3-month outcome	Outcome
1	32.5	3000/10	In-field recurrence	Deceased 5-months post-SBRT
2	59.5	4200/10	Stable	Alive 3.5 years post-SBRT
3	85.5	5574/6	Stable	Alive 3.5 years post-SBRT
4	44.75	3420/6	Lost to imaging follow-up	Alive 2 years post-SBRT

DISCUSSION

- This study suggests a minimum dose threshold that is beyond 30Gy to achieve tumor control.
- SBRT appears to have a good side-effect profile for NEN patients. There was no evidence of RILD, deterioration in liver function or elevation in liver enzymes. Three patients experienced transient fatigue or abdominal discomfort.

- A literature review found no studies on radiation for NEN hepatic metastases. Two studies suggest that pancreatic NEN may be radiosensitive. A 36 patient series found a 90% symptomatic palliation clinical response rate with external beam radiotherapy of unresectable pancreatic NEN primary tumors[1].

- May consider applying non-NEN liver metastases SBRT guidelines for NEN: 3 or fewer lesions ($\leq$ 6cm), at a distance >1.5cm from any luminal GI organ, with minimal prior systemic therapy, in the absence of extra-hepatic disease[3].

- Limitations: this is a small case series with a heterogeneous patient population who had undergone various treatments previously.

CONCLUSIONS

- This study represents the first reported case series of SBRT specifically for neuroendocrine hepatic metastases.

- It appears that SBRT is well tolerated, and may achieve disease stability for a substantial period of time.

- While it is a small case series with a heterogeneous patient group, the results are encouraging.

- Further investigation into the effectiveness of SBRT for neuroendocrine hepatic metastases, progression-free survival, control of tumor functionality and neuropeptide secretion, and determination of selection criteria is warranted.

REFERENCES

[1]Contessa JN, Griffith KA, Wolff E, et al. Radiotherapy for pancreatic neuroendocrine tumors. Int J Radiat Oncol Biol Phys 2009;75:1196.
[2]Lock M, Gaede S, Sinclair K, et al. Phase I study of image-guided and radiobiologically-guided stereotactic body radiotherapy for hepatic lesions. Radiother Oncol. 2010; 96:S12.
[3]Schefter TE, Kavanagh BD. Radiation therapy for liver metastases. Semin Radiat Oncol 2011;21:264-70.