Clinical Outcomes of Stereotactic Radiosurgery for Different Neuroendocrine Tumor Brain Metastases: A Systematic Review

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Background

Neuroendocrine tumor (NET) brain metastases (BM) are rare malignancies which frequently bear a poor prognosis and have the potential to secrete hormones. Optimal treatment approach for NET BM remains unclear, with significant heterogeneity both across and within primary tumor types, and limited outcome data. Given their known differences in clinical course and genetic profile **(Table 1)**, we aim to summarize reports of BM across different NETs treated with SRS.

Table 1. Frequency of mutations in 4 key genes across different neuroendocrine tumors.

Gene	pNETs	LNETs	GI-NETs	PPGLs	Pathway
MEN1	44%	6%	21%	2%	Histone methylation
PTEN	7%	2-7%	13%	7%	PI3K/AKT/PTEN pathway
PI3KCA	1%	0%	9%	1%	PI3K/AKT/PTEN pathway
TP53	3%	9%	64%	0-2.35%	Cellular apoptosis

pNETs = pancreatic neuroendocrine tumors; LNETs = lung neuroendocrine tumors, typical carcinoid; GI-NETs = gastrointestinal neuroendocrine tumors; PPGLs = pheochromocytomas and paragangliomas

Methods

Search strategy: A systematic review of the literature was performed in accordance with PRISMA guidelines.[1] An initial search was performed using Pubmed/MEDLINE, Embase, and Web of Science on 1 July 2024 using the following search strategy ("neuroendocrine tumor" OR "neuroendocrine neoplasm" OR "neuroendocrine carcinoma" OR "NET") AND ("brain metastasis" OR "brain metastases" OR "intracranial metastases") AND ("stereotactic radiosurgery" OR "stereotactic body" OR "CyberKnife" OR "GammaKnife").

Inclusion Criteria: (1) neuroendocrine tumor brain metastases were described; (2) adult patients included; (3) SRS treatment and outcome data were available.

Exclusion criteria: (1) Article not available in English; (2) Review article without case data; (3) Duplicate; (4) Pediatric case (age < 18); (5) SRS was only used for treatment of the primary tumor and not for treatment of BM; (6) Preprint articles; (7) Executive summaries and clinical practice guidelines; (8) Re-analysis of previously published data.

Results

Our search strategy yielded 230 articles. Following exclusion of duplicate records, 138 unique titles were screened. Of these, 28 and 94 were excluded during title and full-text screening, respectively. A full-text review was then performed on the remaining 16 articles, comprising 256 patients. Number of patients per study cohort ranged from 1 to 101 (mean = 16). Ten articles were single case reports. The most commonly investigated primary site was lung (5 studies), followed by the skin (2 case reports) and uterine cervix (2 case reports). Median survival post-SRS ranged from 5 to 42 months. Median tumor volume ranged from 0.08 cm^3 to 33.62 cm^3. Local control results were available in 3 of 6 non-case report studies (2 pulmonary and 1 mixed primary).

Figure. 1. PRISMA flow diagram and search results.

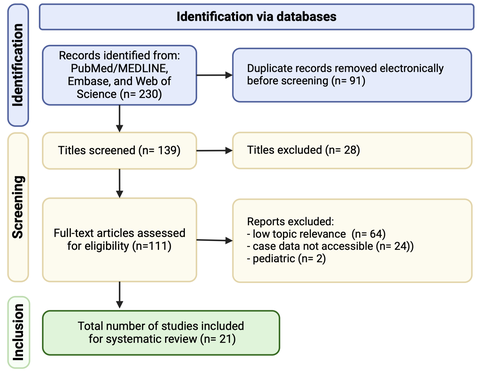

Table 2. Summary of included studies of stereotactic radiosurgery for management of neuroendocrine tumor brain metastases.

Primary site	Study	Year	No. of patients	Median No. of brain metastases	Size of brain metastases	Median dose (Gy)	Local recurrence post-SRS	Median survival post-SRS (months)
Mixed cohort	Prayongrat et al.	2018	33	3	Mean tumor volume: 1.41 cm^3	20	16.70%	6.9
Pulmonary	Kawabe et al.	2016	101	3	Not available	20	13.8% at 12-months post SRS	9.6
Pulmonary	Wegner et al.	2019	68	Not available	Not available	22	Not available	11
Pulmonary	Popov et al.	2023	25	Not available	Not available	Not available	Not available	7
Pulmonary	Koffler et al.	2020	11	Not available	Not available	Not available	Not available	6.1
Pulmonary	Kotecha et al.	2016	8	1.5	Median lesion volume: 4.2 cm^3 (0.08-27.20 cm^3)	20	12.5% for duration of follow-up	20.4
Uterine cervix	Mori et al.	2020	1	10	Volume: 7.0 cm^3	30	Lesion recurred (no time interval specified)	42
Uterine cervix	Brown et al.	2008	1	1	Not available	16	No recurrence	5
Skin (Merkel cell)	Grubb et al.	2021	1	1	Largest diameter: 6.3-cm	Not available	No recurrence	4.5
Skin (Merkel cell)	Gaburak et al.	2023	1	1	Volume: 5.0 cm^3	30	Not available	5
Gastrointestinal	Benjamin et al.	2020	1	14	Volume: 0.25 cm^3	18	No recurrence	12
Retroperitoneal	Yamada et al.	2022	1	2	Largest diameter: 2.7 cm	35	No recurrence	> 11
Lymph node (Merkel cell)	Feletti et al.	2009	1	1	Volume: 33.62 cm^3	25	No recurrence	> 8
Parotid (Merkel cell)	Young et al.	2021	1	2	1.1 × 1.1 cm, larger lesion; no data provided for smaller lesion	35	No recurrence	> 20
Adrenal (Pheochromocytoma)	Miyahara et al.	2017	1	1	Not available	24	No recurrence	> 24 months
Unknown primary	Sano et al.	2020	1	5	Sum of largest diameters of 5 target lesions: 14.2 cm	Not available	Multiple lesions recurred (no time interval specified)	Not available

- Pulmonary NETs represented the largest number of total patients (n = 213) across the reviewed studies
- The median survival post-SRS ranged from 6.1 to 20.4 months. Among these studies, a pulmonary cohort of 101 patients reported a recurrence rate of 13.8 % at 12 months. A case series similarly reported local progression in only 1 of 8 patients.
- The mixed primary study included 33 patients with a median number of 3 BM. The most common primary tumors reported were the lung and cervix, which is consistent with the overall results of our systematic review. In addition, this study reported a long-term local failure rate of 16.7 %.
- Other single case reports included primary sites as follows: 2 uterine cervical, 2 skin, and 1 each of gastrointestinal, retroperitoneal, lymph node, parotid, adrenal, and unknown. Among these patients, a case of neuroendocrine carcinoma of the uterine cervix and a case of unknown primary both had local failure, although neither report included time of local failure post-SRS. Across the remaining cases, local control was reported with follow-up times ranging from 4.5-24 months.

Conclusion

Given the recent increase in age-adjusted incidence of NET BM, determining an optimal treatment approach for these malignancies is of growing importance. Prognosis generally remains poor, with BM being a significant predictor of overall survival. Our review indicated large variability in outcomes both between and within primary tumor types, suggesting a need for further investigation of predictive molecular biomarkers.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery*. 2010;8(5):336-341.

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