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Research

Should Stereotactic Radiosurgery Be Considered for Salvage of Intracranial Recurrence after Prophylactic Cranial Irradiation or Whole Brain Radiotherapy in Small Cell Lung Cancer? A Population-Based Analysis and Literature Review

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ABSTRACT

Background: Prophylactic cranial irradiation (PCI) improves survival and prevents intracranial recurrence (IR) in limited stage (LS) and extensive stage (ES) small cell lung cancer (SCLC). However, despite PCI, IR affects 12%–45%, and limited data exist regarding salvage brain reirradiation (ReRT). We performed a population-based review of IR in SCLC.

Methods: Demographic, treatment, and outcome data of consecutive patients (N = 371) with SCLC assessed at a tertiary cancer centre (01/2013–12/2015) were abstracted, and summary statistics calculated. Kaplan-Meier estimates and univariate and multivariate analysis (MVA) via the Cox proportional hazard model were performed.

Results: Median age was 66.1 years, and 59.8% were Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Median survival was 24 months (95% CI 18.3-29.7 months) for LS (N = 103) and 7 months (95% CI 6.1-7.9 months) for ES (N = 268). 72 of 103 patients with LS and 97 of 214 of those with ES received PCI. 54 of 268 ES presented with brain metastases (BM) of whom 46 of 54 received whole brain RT (WBRT). 18.9% (32/169) recurred post-PCI (13 LS; 19 ES) and 30.4% (14/46) recurred after WBRT. Of those who recurred/progressed after cranial RT, 56.5% (26/46) had <5 BM, 39.1% had no extracranial disease, and 50% were ECOG 0–2. In retrospect, 17 of 46 would have been candidates for salvage stereotactic radiosurgery: 13 post-PCI and 4 post-WBRT.

Conclusions: This cohort challenges commonly held beliefs that IR is always diffuse, associated with clinical deterioration, and synchronous with systemic failure. Approximately 1 in 3 SCLC patients with IR after PCI or WBRT appear clinically appropriate for salvage stereotactic radiosurgery.

RÉSUMÉ

Contexte : L'irradiation crâniale prophylactique (ICP) améliore la survie et prévient la récidive intracrânale (RI) dans le cancer pulmonaire à petites cellules (CPPC) au stade limité (SL) et avancé (SA). Cependant, malgré l'IVP, la RI survient dans 12%–45% des cas, et il n'existe que des données limitées concernant la ré-irradiation du cerveau (ReRT) à des fins de récupération. Nous avons effectué un examen de la RI en CPPC basé sur la population.

Méthodologie : Les données démographiques et les données de traitement et de résultats de patients consécutifs (N = 371) présentant un CPPC évalués dans un centre de cancérologie tertiaire (01/2013–12/2015) ont été extraites et des statistiques sommaires ont été calculées. Des estimations Kaplan-Meier et des analyses à une et plusieurs variables ont été effectuées à l'aide du modèle des risques proportionnels de Cox.

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Ethical Approval: The Health Research Board of Alberta approved this study.

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Résultats : L'âge médian était de 66,1 ans et r9,8% présentaient un EcoG 0–2. La durée de survie médiane était de 24 mois (IC 95% 18,3-29,7 mois) en SL et de 7 mois (IC 95% 6,1-7,9 mois) en SA. &2 patients sur 103 au stade limité et 97 patients sur 214 au stade avancé ont reçu de l'ICP. Parmi les patients au stade limité, 54 sur 268 présentaient des métastases au cerveau (MC) dont 46/54 ont reçu de la radiothérapie du cerveau entier (RTCE). 18,9% (32/169) ont présenté une récidive post-ICP (13 SL; 19 SA) et 14/46 (30,4%) ont présenté une récidive post RTCE. Parmi les patients qui ont eu une récidive ou une progression après RT crâniale, 56,5% (26/46) avaient <5 MC, 39,1% n'avaient aucune maladie extra-crâniale, et 50% avaient un EcoG 0–2. En rétrospective, 17/46 auraient été des candidats à une ReRT de récupération: 13 post-ICP et 4 post-RTCE.

Conclusions : Cette cohorte remet en question les croyances générales selon lesquelles la RI est toujours diffuse, associée à la détérioration clinique, et synchrone avec la défaillance systémique. Environ in patient CPPC sur trois présentant une RI après ICP ou RTCE semble cliniquement approprié pour la ReRT de récupération.

Keywords: Recurrence; prophylactic cranial irradiation; small cell lung cancer; stereotactic radiosurgery

Introduction

Small cell lung cancer (SCLC) accounts for 15%–20% of all lung cancers [1]. SCLC has historically been staged according to whether all disease is encompassable in a tolerable radiotherapy portal (limited stage [LS]) or not (extensive stage [ES]). Patients who have extrathoracic disease at diagnosis by definition are ES and comprise approximately 2/3 of all SCLC [2].

In the absence of prophylactic cranial irradiation (PCI), up to 40% develop brain metastases (BM) within one year, rising to >50%–60% by two years [1,3–6]. PCI remains a standard of care for LS SCLC after completion of initial curative-intent systemic chemotherapy concurrent with radical thoracic radiotherapy (TRT). PCI improves overall survival (OS), disease-free survival, and intracranial control in LS disease [6]. PCI also significantly reduces the incidence of symptomatic intracranial metastases in ES disease after systemic chemotherapy, with <4% acute grade ≥3 adverse events and 2% rate of severe late effects [7].

Reported intracranial recurrence (IR) rates after PCI range from 12% to 45%, typically occurring between 4 and 24 months after radiotherapy [4,7–12]. Treatment options include best supportive care (BSC) and consideration of reirradiation (ReRT) via whole brain radiotherapy (WBRT) [13], given the long-held presumption that IR heralds both diffuse subclinical intracranial disease [14] and simultaneous systemic failure [15]. However, WBRT after PCI raises concerns about acute toxicity and therefore short-term detrimental impact on quality of life (QOL), in addition to uncertain effects on symptoms, cognition, and OS [16].

Depending on whether staging imaging is cranial CT or MRI, 10%–24% of ES patients have BM at diagnosis [5,17,18]. If symptomatic, patients are usually offered WBRT up front [15,17–19], which has a response rate of 50%–55% [20]. The median survival (MS) of patients with untreated BM is 6–12 wk [21], rising to 4–10 months after treatment, depending in part on extracranial disease extent and control [6,18,20,22].

As there are limited available data regarding techniques, dose, or outcomes of ReRT [14,17,23], our purpose was to perform a population-based review of outcomes following IR after either PCI or first-line WBRT.

Methods

Data Collection

Consecutive patients with pathologically or cytologically proven SCLC assessed (01/2013–12/2015) at the Cross Cancer Institute, a tertiary cancer centre, were retrospectively reviewed. This timeframe captured current treatment techniques while ensuring sufficient available follow-up. Data abstracted from the electronic and paper medical record included anonymized clinical (age, gender, smoking status, stage, performance status [PS]), treatment (systemic therapy, TRT), and outcomes (disease progression/recurrence, toxicity, OS). Patients were analyzed within cohorts based on stage and intracranial status at diagnosis (Appendix A). Institutional review board approval was obtained from the Health Research Board of Alberta with patient consent waived.

Patients were retrospectively evaluated for stereotactic radiosurgery (SRS) eligibility at IR based on the 2017 Cancer Care Alberta clinical practice guideline *Brain Oligometastases* [24]. Criteria required for SRS for non-SCLC histology listed include Karnofsky PS of 70 or greater (ECOG PS 0–2); 4 or fewer metastases; largest metastasis less than 4 cm; and controlled, controllable, or absent systemic disease.

Data Analysis

Summary statistics were performed for the overall population and three subcohorts. Mean and standard deviations were reported for continuous variables, frequency, and proportions for categorical variables. Kaplan-Meier estimates and corresponding 95% confidence intervals were obtained for OS. Univariate and multivariate analysis (MVA) for OS were analyzed using Cox's proportional hazard model, with hazard ratios (HRs) and the corresponding 95% confidence interval reported. A *P*-value of <.05 was used for statistical significance. SPSS, version 23, was used to conduct all the statistical analysis.

Table 1
Limited Stage Patients Subclassified by PCI Status

Parameter	PCI (N = 72)	No PCI (N = 31)	*P* Value	Overall (N = 103)
Age at diagnosis				
<50 y	2 (2.8%)	2 (6.5%)	.38	4 (3.9%)
50–59 y	20 (27.8%)	4 (12.9%)	.10	24 (23.3%)
60–69 y	27 (37.5%)	9 (29.0%)	.41	36 (35.0%)
70–79 y	21 (29.2%)	11 (35.5%)	.53	32 (31.1%)
>80 y	2 (2.8%)	3 (9.7%)	.38	5 (4.9%)
Unknown	-	2 (6.5%)	-	2 (1.9%)
Gender				
Male	34 (47.2%)	11 (35.5%)	.27	45 (43.7%)
Female	38 (52.8%)	20 (64.5%)	.27	58 (56.3%)
Smoking status				
Current smoker	39 (54.2%)	16 (51.6%)	.81	55 (53.4%)
Ex-smoker	32 (44.4%)	14 (45.2%)	.95	46 (44.7%)
Never smoker	1 (1.4%)	0	-	1 (1.0%)
Unknown	-	1 (3.2%)	-	1 (1.0%)
ECOG at diagnosis				
0–2	55 (76.4%)	16 (51.6%)	**.013**	71 (68.9%)
3–4	3 (4.2%)	4 (12.9%)	.11	7 (6.8%)
Unknown	14 (19.4%)	11 (35.5%)	.08	25 (24.3%)

ECOG, Eastern Cooperative Oncology Group performance status; Gy, Gray; PCI, prophylactic cranial irradiation; RT, radiation therapy.
Bolded *P*-value of <.05 indicates statistical significance.

Table 2
Extensive Stage Patients Subclassified by Intracranial Status at Diagnosis and PCI Delivery

Parameter	ES Without BM at Diagnosis			With BM	Overall (N = 268, %)
	PCI (N = 97, %)	No PCI (N = 117, %)	*P* Value	BM* (N = 54, %)	
Age at diagnosis					
<50 y	6 (6.2%)	6 (5.1%)	.75	2 (3.7%)	14 (5.2%)
50–59 y	30 (30.9%)	15 (12.8%)	**.001**	14 (25.9%)	59 (22.0%)
60–69 y	39 (40.2%)	41 (35.0%)	.47	18 (33.3%)	98 (36.6%)
70–79 y	16 (16.5%)	34 (29.1%)	**.04**	17 (31.5%)	67 (25.0%)
≥80 y	4 (4.1%)	15 (12.8%)	**.025**	2 (3.7%)	21 (7.8%)
Unknown	2 (2.1%)	6 (5.1%)	.23	1 (1.9%)	9 (3.4%)
Gender					
Male	42 (43.3%)	65 (55.6%)	.06	23 (42.6%)	130 (48.5%)
Female	55 (56.7%)	52 (44.4%)		31 (57.4%)	138 (51.5%)
Smoking status					
Current	51 (52.6%)	59 (50.4%)	.81	24 (44.4%)	134 (50%)
Ex-smoker	44 (45.4%)	54 (46.2%)	.97	0	98 (36.6%)
Never	2 (2.1%)	1 (0.9%)	.46	29 (53.7%)	32 (11.9%)
Unknown	0	3 (2.6%)		1 (1.9%)	4 (1.5%)
ECOG at diagnosis					
0–2	66 (68.0%)	57 (48.7%)	**.004**	27 (50%)	150 (56.0%)
3–4	5 (5.2%)	30 (25.6%)	**<.0001**	14 (25.9%)	49 (18.3%)
Unknown	26 (26.8%)	30 (25.6%)	.88	13 (24.1%)	69 (25.7%)
Extrathoracic disease					
Single site	28 (28.9%)	33 (28.2%)	.95	14 (25.9%)	75 (28.0%)
Multiple sites	32 (33.0%)	44 (37.6%)	.45	40 (74.1%)	116 (43.3%)
None/ unknown	37 (38.1%)	40 (34.2%)	.49	-	77 (28.75)

BM, brain metastases; ECOG, Eastern Cooperative Oncology Group performance status; Gy, Gray; PCI, prophylactic cranial irradiation; RT, radiation therapy; UNK, unknown; WBRT, whole brain radiotherapy.
Bolded *P*-value of <.05 indicates statistical significance.
* 46 of 54 received WBRT up front.

Table 3
First Line Treatment

Parameter	Limited Stage		ES without Brain Metastases		ES with Brain Metastases	Overall (N = 371, %)
	(N = 103)		(N = 214)		(N = 54)	
	PCI (N = 72, %)	No PCI (N = 31, %)	PCI (N = 97, %)	No PCI (N = 117, %)		
Chemotherapy	72 (100%)	24 (77.4%)	97 (100%)	76 (65.0%)	40 (74.1%)	309 (83.3%)
Thoracic RT	61 (84.7%)	17 (54.8%)	71 (73.2%)	34 (29.1%)	19 (35.2%)	202 (54.4%)
Radical intent	52 (85.2%)	9 (29.0%)	-	-	-	61 (16.4%)
POP	-	-				
Wedge pair	1 (1.9%)	-				
3 Field	24 (46.2%)	4 (44.4%)				
4 Field	19 (36.5%)	3 (33.3%)				
5–8 Fields	6 (11.5%)	2 (22.2%)				
SBRT	2 (3.8%)	-				
Palliative intent	9 (12.5%)	8 (25.8%)	71 (73.2%)	34 (29.1%)	19 (35.2%)	141 (38.0%)
POP	8 (88.9%)	4 (50%)	60 (84.5%)	30 (88.2%)	17 (89.5%)	
Wedge pair	-	-	1 (1.4%)	0	-	
3 Field	-	2 (25%)	6 (6.2%)	2 (5.9%)	1 (5.3%)	
4 Field	1 (11.1%)	2 (25%)	4 (5.6%)	1 (2.9%)	1 (5.3%)	
Unknown	-	-	-	1 (2.9%)	-	
No thoracic RT	11 (15.3)	14 (45.2%)	26 (26.9%)	83 (70.9%)	35 (64.8%)	169 (45.6%)
PCI						
12.5 Gy/5	-		2 (2.1%)			2 (0.5%)
15 Gy/3			1 (1.0%)			1 (0.3%)
20 Gy/5	-	-	3 (3.1%)	-	-	3 (0.8%)
25 Gy/10	71 (98.6%)	-	91 (93.8%)	-	-	162 (43.7%)
30 Gy/15	1 (1.4%)	-	-	-	-	1 (0.3%)
WBRT*						
20 Gy/5	-	-	-	-	37 (80.4%)	37 (10.0%)
25 Gy/10	-	-	-	-	3 (6.5%)	3 (0.8%)
30 Gy/10	-	-	-	-	3 (6.5%)	3 (0.8%)
Other	-	-	-	-	3 (6.5%)	3 (0.8%)

Gy, Gray; PCI, prophylactic cranial irradiation; POP, parallel opposed pair; RT, radiation therapy; SBRT, stereotactic body radiation therapy; WBRT, whole brain radiotherapy; WBRT, whole brain radiotherapy.

* 46 of 54 with brain metastases at diagnosis received WBRT.

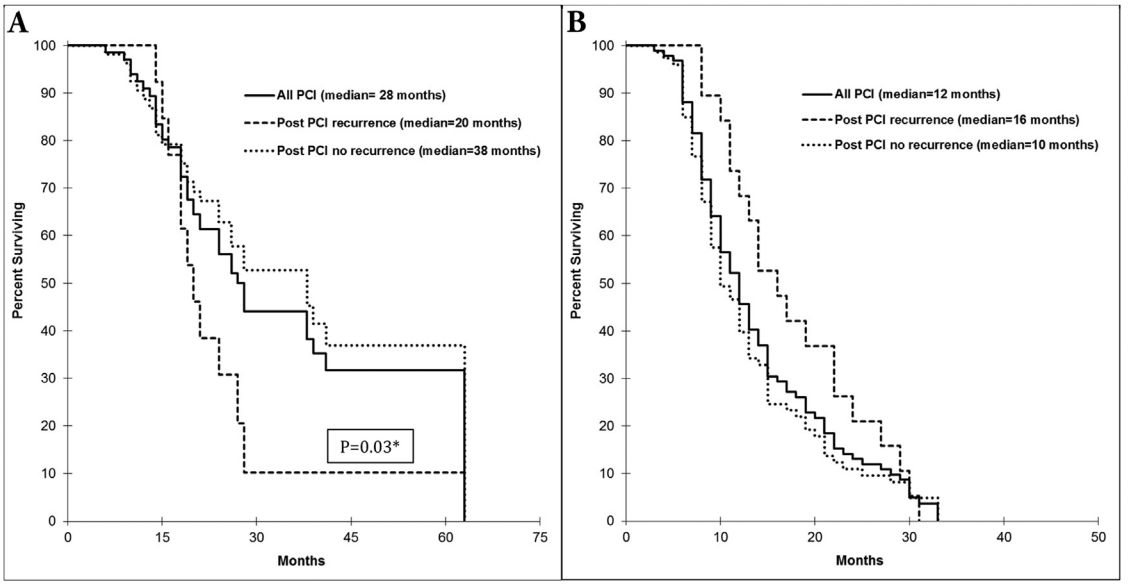

Figure 1. (A) Survival for limited stage patients receiving PCI (overall MS 28 mo [95% CI 23.7-32.3 mo]) and by intracranial recurrence: MS 38 mo (95% CI 25.5-50.5 mo) if no IR vs 20 mo (95% CI 16.5-23.5 mo) with IR (*$P = .03$). (B) Survival for extensive stage patients receiving PCI overall (MS 12 mo [95% CI 10.1-13.9 mo]) and subdivided by IR: MS 16 mo (95% CI 11.7-20.3 mo) if no IR vs 10 mo (95% CI 8.1-11.9 mo) if recurrence. PCI, prophylactic cranial irradiation; MS, median survival; IR, intracranial recurrence.

Table 4
Characteristics of Intracranial Recurrence

Parameter	LS Post-PCI (N = 13)		ES Post-PCI (N = 19)		ES Post-WBRT (N = 14)		Total (n = 46)	
	N	%	N	%	N	%	N	%
Time to IR								
Median† (range)	11.5 (6.9–60.9) mo		8.5 (2.7–26.4) mo		5.8 (1.5–15.7) mo		N/A	
Number of BM								
1	4	30.8	4	21.1	4	28.6	12	26.1
2–4	4	30.8	6	31.6	4	28.6	14	30.4
5–10	0	0	3	15.8	0	0	3	6.5
Other*	3	23.1	6	47.4	6	42.9	15	32.6
UNK	2	15.4	0	0	0	0	2	4.3
Size								
Median (cm)	3.3	-	1.4	-	1.7	-	1.7	-
UNK	6	46.1	7	36.8	4	28.6	17	37.0
ECOG								
0–2	7	53.8	10	52.6	6	42.9	23	50.0
3–4	0	0	3	15.8	2	14.3	5	10.9
UNK	6	46.2	6	31.6	6	42.9	18	39.1
Symptoms								
Fatigue	2	15.4	0	0	1	7.1	3	6.5
Headache	4	30.8	4	21.1	1	7.1	9	19.6
Nausea +/− vomiting	2	15.4	0	0	0	0	2	4.3
Neurological deficit	7	53.8	15	78.9	8	57.7	30	65.2
Asymptomatic	2	15.4	3	15.8	1	7.1	6	13.0
Extracranial recurrence	4	30.8	15	78.9	9	64.3	28	60.9

BM, brain metastases; ECOG, Eastern Cooperative Oncology Group performance status; Gy, Gray; PCI, prophylactic cranial irradiation; RT, radiation therapy.
* Multiple, innumerable, or extensive.
† Measured from first day of initial cranial RT.

Results

A total of 371 patients met eligibility criteria. The median age at diagnosis was 66.1 years, 196 (52.8%) were female, 362 (97.6%) current or ex-smokers, and 222 (59.8%) had baseline ECOG PS 0–2. 103 (27.8%) were LS (Table 1). 268 of 371 (72.2%) were ES: 214 of 268 without BM and 54 of 268 with BM at diagnosis (Table 2). Median follow-up was 9 months (range 0–143 months). As of the date of analysis, 58.3% of LS and 94.4% of ES patients were deceased. MS for LS was 24 months (95% CI 18.3-29.7 months) and for ES was 7 months (95% CI 6.1-7.9 months).

First Line Treatment

For LS patients, 22 (21.4%) received chemotherapy alone, 4 (3.9%) TRT alone, 74 (71.8%) had both, and 3 (2.9%) had no treatment (Table 3). 72 of 103 (71.3%) received PCI. Reasons for not receiving PCI were as follows: 11 of 31 declined; 8 of 31 poor PS; 6 of 31 recurred or died before PCI could be offered; and unknown in 6 of 31. For patients with ES disease, 101 (37.7%) received chemotherapy alone, 12 (4.5%) TRT alone, 112 (41.8%) had both, and 43 (16.0%) had no treatment (Table 3). 97 of 214 received PCI. Reasons for ES patients not receiving PCI were as follows: 27 of 117 declined; 34 of 117 poor PS; 9 of 117 recurred or died before PCI could be offered; 1 of 117 previous RT; and unknown in the remainder. Survival of LS and ES patients who underwent PCI is shown in Figure 1.

Patients who did not have BM at diagnosis but did not receive PCI had a MS of 5 months (95% CI 3.9-6.1 months).

Of 54 ES patients with BM at diagnosis, 27.8% had one metastasis, 25.9% had 2–4, and the remainder had >4 BM. The median size was 2 cm. MS of those with BM at diagnosis was 6 months (95% CI 3.7-8.3 months). 85.2% had WBRT (Table 3), and the remaining BSC only.

Intracranial Recurrence

65 patients recurred in the brain: 13 of 72 LS after PCI; 19 of 97 ES after PCI; 14 of 46 after WBRT for BM; and 19 of 148 (4 LS; 15 ES) after no previous RT (Appendix B), the majority of whom were symptomatic (Table 4). Survival by stage and IR status is shown in Figure 1.

Patients with LS who had not undergone PCI survived a median of 15 months (95% CI 11.1-18.9 months) in the absence of intracranial recurrence, vs. 8 months (95% CI 1.1-14.9 months) after diagnosis of BM. ES patients without PCI who experienced in-brain failure had a MS of 11 months (95% CI 9.1-12.9 months) compared with 4 months for those without (95% CI 3.0-5.0 months).

Those who recurred/progressed in the brain after WBRT had a MS of 9 months (95% CI 6.7-11.3 months) compared with those who did not (MS 11 months, 95% CI 8.9-13.1 months).

Table 5
Literature Comparison

Reference	Patients	SRS Technique	Eligibility Criteria for SRS	Previous PCI or WBRT	Follow-up	Toxicity	Outcomes
Bernhardt 2018 [31]	N = 5	NS	• NS	5/5 WBRT	Clinical examination q8–12 wks; MRI recommended	NR	MS 10 mo after SRS
Bragstad 2017 [43]	N = 5	Mean marginal dose 20.4 Gy Frame-based Gamma Knife	• KPS ≥70 • 1–6 BM • Total tumour volume ≤25 cc • No prior SRS	0	Phone call at 1 mo then q3 mo + MRI at 1,3,6,9, and 12 mo	NR	OS not significantly different from NSCLC; SRS not reported separately
Bernhardt 2016 [14]	N = 13	18–24 Gy to 80% IDL Mask-Based CTV = 2 mm	• 1–4 BM	13/13 PCI Median 30 Gy/15	NR	All grade 1–2	MS 5 mo after SRS
Ozawa 2015 [9]	N = 25	Various	• Limited stage • CR or good PR to chemo • Baseline PET	7/25 PCI 18/25 none	MRI preferred	NR	NR
Rava 2015 [17]	N = 40 (132 lesions)	40.2% of lesions <16 Gy Frame-based Gamma Knife	• KPS > 70 • No repeat WBRT • Extracranial disease permitted (active in 60%)	27/40 WBRT 10/40 PCI 3/40 Other	MRI q2–3 mo	No grade 4/5 12.5% necrosis on imaging 5% required steroids 0% resection for radionecrosis	MS 6.5 mo from SRS 1y OS 35% 1y LC 69% 1y distant in-brain recur 78%
Yomo 2015 [3]	N = 70 (292 lesions)	Median 20 Gy (range 12–22 Gy) Frame-based Gamma Knife CTV = 1–2 mm	• De novo: 1–10 BM and any number of recurrent BM • Intracranial failure after WBRT • Enhancement of CN, ventricular ependymal layer or cortical surface not permitted • Extracranial disease permitted (active in 64%)	7/70 PC I8/70 surgery 16/70 WBRT 1/70 EBRT	Clinical examination + MRI q1–3 mo	0 grade 3 toxicity 3/70 steroids + hyperbaric 02 for late radionecrosis	MS after SRS 7.8 mo 1y OS after SRS 43% 2y OS after SRS 15% 1y neurologic death-free survival 94% 1y distant in-brain recurrence 47% 1y local failure 23% 17% salvage WBRT
Li 2014 [10]	N = 45 (68 lesions)	30 Gy to 90% IDL Mask-based Linac FSRT	• No leptomeningeal carcinomatosis	35/45 WBRT; median 40 Gy/20	MRI at 1–3 mo then q3–6 mo	4.3% symptomatic intracranial edema	MS 10 mo from SRS LC 98% at 6 mo; 72% at 12 mo 40% neurologic death 26% in-brain failure at median 5 mo

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Table 5 (*continued*)

Reference	Patients	SRS Technique	Eligibility Criteria for SRS	Previous PCI or WBRT	Follow-up	Toxicity	Outcomes
Yomo 2014 [29]	N = 41 (121 lesions)	20 Gy (range 10–22 Gy) Frame-based Gamma Knife	• 1–10 lesions • Enhancement of CN, ventricular ependymal layer, or cortical surface not permitted • Extracranial disease permitted (active in 61%)	0/41	Clinical examination + MRI q1–3 mo	6% delayed radiation injury/local recurrence at a median of 10.8 mo; 2 pts had grade 3 symptomatic delayed injury requiring steroids and hyperbaric 02	MS 8.1 mo OS at 1 y 44% 5% neurologic death at 1 y 14% local failure at 1 y 22% distant in-brain failure at 6 mo; 44% at 1 y 15% salvage WBRT 44% salvage SRS
Kuremsky 2013 [41]	N = 31	20 Gy (range 11–24 Gy) Frame-based Gamma Knife	• 1–8 lesions • Any RPA	26/31 PCI	MRI at 6 wks then q3 mo	5/31 radionecrosis; 4/5 required surgery	MS 5.9 mo; OS 20% at 1 y 19% local failure 36% distant failure; freedom from neuro death 40% at 1 yr
Harris 2012 [28]	N = 51	18 Gy (range 10–24 Gy) Frame-based Gamma Knife	• Any number of BM • Extracranial disease permitted (active in 29%)	35/51 WBRT 16/51 PCI	MRI at 4–8 wk then q3mo	2 pts: symptomatic RT necrosis, 1 req surgery 1 pt: admitted for IV steroids 1 pt: long-term outpt steroids	MS 5.9 mo 1y OS 24% 1y freedom from local failure 57% Median TTLF 8.7 mo 1y distant in-brain failure 58% median 3 mo
Olson 2012 [44]	N = 27	20.5 Gy (range 15–24 Gy) Mask-based CyberKnife	• Extracranial disease permitted (active in 85%)	19/27 WBRT 8/27 PCI	Clinical examination + MRI at 2 mo then q2–3 mo x 1 y, then q3–6 mo	No treatment-related toxicities No patient required steroids after SRS	MS 3 mo from SRS; 25% 6 mo OS from SRS LC at 6 mo 76.5% 6.3% CR 62.5% distant in-brain failure at median 3.5 mo
Wegner 2011§ [32]	N = 44 (128 lesions)	18 Gy to 50% IDL (range 14–20 Gy) Frame-based Gamma Knife	• Extracranial disease permitted (active in 54%)	9/44 PCI 3/44 PCI + WBRT 24/44 WBRT (median 30 Gy/10) 8/44 None	MRI at 2 mo then q3mo x 1 y, then q4–6 mo	2.2% transient peritumoural steroid-responsive edema	MS 9 mo from SRS; 87% of patients had ≥2 mm decrease at a median of 2 mo; 5 pts had local failure; 2/5 required surgery; 90% LC at 6 mo; 86% LC at 12 mo; 61% distant in-brain failure at a median of 7 mo
Pan 2005 [45]	N = 20 (39 lesions)	18 Gy (range 3–24 Gy) Frame-based Gamma Knife	• NR	74.3% received combined WBRT + SRS†	Clinical examination q1–3 mo MRI + contrast q3–6 mo	No "direct complications"	MS 16 mo LC 81% at 6 mo†

(*continued on next page*)

Table 5 (*continued*)

Reference	Patients	SRS Technique	Eligibility Criteria for SRS	Previous PCI or WBRT	Follow-up	Toxicity	Outcomes
Sheehan 2005 [37]	N = 27	16 Gy (range 13–20 Gy) Frame-based Gamma Knife	• Recurrent BM or unresectable new BM after fractionated RT • 1–6 BM • ≤3 cm • Extracranial disease permitted	27/27 Median dose 30 Gy (range 24–56 Gy)	MRI or CT at 2 mo then q3 mo x 1 y, then q4–6 mo	No treatment-related mortality	MS 4.5 mo from SRS LC 81%* Local progression 7.4% Distant in-brain failure 11%
Serizawa 2002 [40]	N = 34	21 Gy (range NR) Frame-based Gamma Knife	• ≤25 BM • Max of 3 BM ≥2 cm • No surgically inaccessible tumor ≥3 cm‡ • Life span >3 mo • Extracranial disease permitted (active in 79.4%)	0/34	Clinical examination + MRI q1–3 mo	No "acute brain swelling"	Mean survival 9.1 mo 1-y tumour control rate 94.5% Mean time free from new lesions 6.9 mo 2/34 received salvage WBRT
Hoffman 2001 [46]	N = 13 (32 lesions)	18 Gy (range NR) Frame-based Gamma Knife	• KPS ≥70 • Max size ≤3 cm • New diagnosis or recurrent • Extracranial disease permitted	11/13 Median dose 37.5 Gy (range 24–50 Gy)	Clinical examination + MRI q3 mo	7%† symptomatic cerebral edema (1 pt required surgery) 5%† symptomatic RT necrosis (3 pts required surgery)	MS 12 mo overall (MS 5.9 mo for recurrent lesions)
Li 2000 [47]	N = 5	20 Gy (range 15–35 Gy) Frame-based Linac	• KPS ≥60 • Solitary BM • ≤4.5 cm • Life span ≥3 mo • Extracranial disease permitted	Not specified	Contrast-enhanced CT q2–3 mo Median follow-up 8 mo	Acute toxicity not evaluated No serious late complications reported	Not separately reported for SCLC

BM, brain metastases; CN, cranial nerves; CR, complete response; CT, computed tomography; CTV, clinical target volume; FSRT, fractionated stereotactic radiosurgery; IDL, isodose line; KPS, Karnofsky Performance Status; LC, local control; MRI, magnetic resonance imaging; MS, median survival; NR, not reported; PCI, prophylactic cranial irradiation; PET, positron emission tomography; PR, partial response; SCLC, small cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

* 81% of tumours (86% of patients).

† Includes non-SCLC and SCLC patients, and control rate by lesion.

‡ All tumours >3 cm were resected before SRS.

§ Update of Sheehan 2005.

Table 6
Prognostic Factors

Reference	Significantly Improved Survival	No Association with Survival	Significantly Improved Local Control	No Association with Local Control
Bernhardt 2016 [14]	• KPS≥50	• GPA score • Age • Extracranial progression • RPA class • Number of BM	NR	NR
Rava 2015 [17]	• Controlled extracranial disease (vs uncontrolled)	• Previous PCI vs WBRT • Gender • Number of BM	• Dose ≥16 Gy (vs <16 Gy) • BM ≤2 cm (vs >2 cm)	• Number of BM
Yomo 2015 [3]	• KPS ≥90 • Solitary BM	• Age • Controlled extracranial disease • Prior WBRT/PCI • Post SRS chemotherapy	• No prior WBRT • Marginal dose >20 Gy	• Target volume • Focal deficit
Yomo 2014 [29]	• KPS ≥90 • Post-SRS chemotherapy	• Age • Extracranial disease status • Number of brain metastases • Total PTV	NR	NR
Li 2014 [10]	• Pre-treatment RPA class • Stage of primary	• Age • Number of metastases • KPS • GPA • Interval before brain metastases diagnosis • Systemic disease • Tumour volume • Symptom status • Number of chemotherapy cycles	NR	NR
Kuremsky 2013 [41]	• Lack of widespread metastatic disease	• Age • Time from diagnosis of primary	• Non–small cell histology vs SCLC	NR
Harris 2012 [28]	• Absence of extracranial disease (vs stable or progressive) • Chemotherapy after SRS	• Number of BM • Marginal dose	• Chemotherapy within 3 wk of SRS • Solitary BM • Age	• Gender • WBRT vs PCI
Olson 2012 [44]	None found	None found	None found	None found
Wegner 2011 [32]	• KPS • Received both SRS + WBRT within 4 wk	• Age • Active systemic disease • Total tumour volume • Tumour volume ≥7cm^3 • Time to BM diagnosis • Number of BM	NR	NR
Pan 2005* [45]	• Age <65 y • KPS ≥70 • No preexisting neurologic deficits • More than one SRS treatment • Pre-SRS craniotomy	• Previous WBRT • SCLC vs NSCLC histology	• Tumour volume <2 cm^3 • Absence of cystic component • Margin dose >14 Gy • No previous WBRT	NR
Sheehan 2005 [37]	• Pre-SRS KPS ≥90 • Decreased tumour volume (≤1.8 cm^3 vs >1.8 cm^3) • Increased time from diagnosis of SCLC to diagnosis of BM (≥15 mo vs <15 mo)	• Number of brain metastases • Location of brain metastases	NR	NR

(*continued on next page*)

Table 6 (*continued*)

Reference	Significantly Improved Survival	No Association with Survival	Significantly Improved Local Control	No Association with Local Control
Seriwaza 2002* [40]	• Female • KPS ≥70 • Controlled extracranial disease	• Age • SCLC vs NSCLC • ≤10 vs >10 BM • Max size ≥25 mm vs <25 mm • Leptomeningeal disease • Chemotherapy • Microsurgery	NR	NR
Hoffman 2001* [46]	• Newly diagnosed BM • Absence of extracranial metastases • Fewer brain metastases • Adenocarcinoma vs other histologies Recurrent BM • Better KPS • Fewer brain metastases • Control of the primary • Adenocarcinoma vs other histologies	• Newly Diagnosed BM • Adding WBRT to SRS • Age • KPS • Control of the primary • RPA score • Synchronous vs metachronous diagnosis of BM • Total target volume	• Smaller total target volume • Higher SRS dose • Homogeneous enhancement	• Adding WBRT to SRS • Newly diagnosed vs recurrent BM

BM, brain metastases; CN, cranial nerves; CR, complete response; CT, computed tomography; CTV, clinical target volume; FSRT, fractionated stereotactic radiosurgery; IDL, isodose line; KPS, Karnofsky Performance Status; LC, local control; MRI, magnetic resonance imaging; MS, median survival; NR, not reported; PCI, prophylactic cranial irradiation; PET, positron emission tomography; PR, partial response; SCLC, small cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

* Combined NSCLC and SCLC population.

On MVA, for patients receiving PCI, the time interval between brain radiotherapy courses predicted OS (HR 0.87; $P < .001$), whereas baseline disease stage (HR 3.56; $P = .008$) and initial cranial RT dose predicted IR (HR 0.65; $P = .047$) (Appendix C).

ReRT and SRS Eligibility

30 of 46 patients were reirradiated at the time of recurrence/progression, of whom one received SRS and two had fractionated SRS (Appendix D). Based strictly on the 2017 Cancer Care Alberta clinical practice guideline criteria described previously, 6 of 46 patients (13.0%) were apparent candidates for salvage SRS. However, taking into account emerging data suggesting that patients with 10 BM or more experience similar outcomes [25–27], putative eligibility criteria could be expanded. When PS was not explicitly reported, for some patients it could be estimated based on described symptom burden and function (similar to [14]). Moreover, although patients with uncontrolled extracranial disease are not optimal candidates for SRS, those going on to second line systemic therapy or clinical trial have not yet exhausted all systemic treatment options; therefore, the possibility exists that extracranial disease could still be controllable. Thus, modified inclusion criteria including patients with up to 10 BM, good PS, and those who received second line chemotherapy revealed 17 (37.0%) who appear to have been candidates for salvage SRS: 5 LS patients post-PCI; 8 ES post-PCI; and 4 ES patients post-WBRT.

Discussion

PCI reduces the incidence of BM by 50%–80% regardless of disease stage at diagnosis [12,17], but recurrence after PCI is common [3,8,12,28]. We report intracranial recurrence rates of 18.1% and 19.4% after PCI in LS and ES disease, respectively, and 30.4% recurring or progressing after WBRT for established BM. Patients without BM at diagnosis who did not undergo PCI had an IR rate of 12.8%, lower than the 32% reported in a systematic review of IR in the absence of PCI [12].

Based on the Disease-Specific Graded Prognostic Assessment, factors signifying the best prognosis for patients with SCLC at initial diagnosis of BM are Karnofsky PS 90–100, age <50, solitary BM, and no extracranial metastases [22]. Patients with all 4 of these good risk factors had a MS of 17.1 months (range 6.1–27.4 months) with survival after combined modality therapies (WBRT + SRS; surgery + WBRT; surgery + WBRT + SRS) significantly superior to WBRT alone [22]. The Disease-Specific Graded Prognostic Assessment excluded recurrent BM, and therefore the efficacy of salvage therapy was not evaluated [22], but patients with BM refractory to WBRT have a life expectancy of fewer than two months [20].

Management of IR is critical for disease control and QOL [3,17,23,28] and decreases rates of neurologic death [29]. In the landmark EORTC trial of PCI for ES disease, 16.8% (24/143) recurred in the brain after PCI, with 2/24 reirradiated [7], whereas in the recent Japanese randomized trial employing close MRI follow-up, 47.8% (54/113) recurred in the

brain after PCI, of whom 25 (46%) received reirradiation [8]. Optimal treatment remains controversial, in part because results of local brain therapy are confounded by the competing risks of systemic progression and intercurrent mortality [29,30].

Studies of repeat WBRT are largely retrospective single-institution case series of limited patient numbers, with retreatment doses of 20–25 Gy and post-ReRT MS of 2–5 months [13,14,23,31]. Symptom improvement rates after repeat brain RT range from 40% to 70%, whereas neurologic function improves in 30%–40% and stabilizes in approximately 40% [13,14,23]. 10% cannot complete the full prescribed course of ReRT [13,14]. One-third do not report ReRT side effects [13]; however, the irreversible neurocognitive decline risked with one course of WBRT is likely to be exaggerated after ReRT [28,32]. Overall, repeat WBRT is unlikely to offer durable control [17].

Whether outcomes after ReRT differ depending on whether the first brain RT course was prophylactic or therapeutic is not definitively known. Scharp et al found no statistically significant difference in MS [13]. However, Harris et al described that patients failing after PCI trended toward neurologic death (HR 4.3, $P = .06$) compared with those who failed after WBRT for BM: 8 of 12 (67%) vs. 10 of 30 (33%), respectively [28]. The authors surmised that those receiving PCI were likely to have had a greater response to first line therapy, potentially due to a lower burden of systemic disease at baseline, given that PCI administration is limited to those with LS and chemotherapy-responsive ES disease [28].

Systemic therapy alone or combined with WBRT have been explored as alternatives for treatment of BM in SCLC. Improvement in neurologic and/or functional status is seen in 40%–50% [15,33], with PS stability in another 20% [15]. Intracranial response rate was 57% with combined chemotherapy and WBRT vs. 22% after teniposide alone ($P < .001$), with 4%–11% grade 3–4 adverse events [15]. Historically fewer than half of patients are suitable candidates for second line chemotherapy, with most pursuing BSC only [34,35]. In our cohort, of the patients who progressed extracranially after first line chemotherapy, 73 (45.6%) received second line systemic treatment. However, in the recent phase III randomized trial of PCI vs. observation in ES disease, 89% went on to second line chemotherapy and a significant proportion of those third or fourth line therapy [8].

SRS delivering high-dose, precisely targeted single-fraction irradiation to visible BM eradicates tumour cells to maximize local control while preserving surrounding normal structures [36,37]. SRS spares patients from high cumulative integral brain radiation doses, decreasing the likelihood of cognitive and other toxicity [3,26,31,32,38] and delaying or avoiding WBRT [39]. SRS may improve PS long enough to allow initiation of systemic therapy for extracranial disease and facilitates continuation of ongoing chemotherapy due to its short administration time [14,23,26]. In other primary histologies, SRS is being increasingly used for salvage of five or more BM, as emerging evidence suggests that efficacy depends more on total volume than absolute number [27].

To date, there has been reticence to utilize SRS in SCLC in part due to the presumption that diffuse microscopic metastases already exist once IR is diagnosed [3,14,28,29,40]. In our study, 56.5% (26/46) had 1–4 BM and 3 of 46 had 5–10 at recurrence. In the cohort of Kuremsky et al, 84% of whom had had previous PCI, 68% had 1 lesion and 23% had 2–4 at salvage SRS [41]. In a modern series of 238 patients, all staged with MRI, an average of 6.3 BM per patient were diagnosed, with 63% having 1–3 lesions [42]. Published data on outcomes of SRS for IR after PCI and WBRT are summarized in Tables 5 and 6.

There were several limitations to our study. As a retrospective analysis, data available for abstraction were limited to medical record documentation. IR was not commonly diagnosed by contrast-enhanced MRI; thus, extent of disease at recurrence may have been underestimated. Lack of radiologic information on size and number of BM was the main reason why SRS eligibility could not be definitively ascertained retrospectively. PS was inconsistently documented and therefore was retrospectively assigned in some circumstances based on recorded symptoms and functional information, after Bernhardt et al [14]. Status of the primary site and regional lymph nodes was not consistently available. Selection bias must be taken into account in relation to outcomes, as patients who underwent surveillance, follow-up imaging, and treatment of IR would not be representative of the entire population [3].

However, our study has strengths in comparison with other published cohorts, many of which do not report SCLC stage at diagnosis, PCI dose-fractionation schedule, reasons why PCI was not received, ReRT techniques, and details around systemic therapy. In others, patients treated for in-brain relapse were analyzed together with those presenting with BM, when there are likely systematic biological differences between these groups [15].

Conclusions

Based on emerging eligibility criteria in non-SCLC histologies, approximately 1 in 3 patients with SCLC who experience in-brain recurrence after PCI or WBRT appear to be candidates for salvage SRS. Treatment of recurrent BM should be individualized based on PS, extent/control of extracranial disease, volume of BM, symptom burden, previous therapy, and patient wishes. SRS benefits of decreased toxicity and minimal interruption of systemic therapy optimize continuity of care and QOL. Further data are required to clearly elucidate local control and survival benefits; however, SCLC patients who are clinically appropriate should be offered salvage SRS for intracranial recurrence post-PCI or WBRT.

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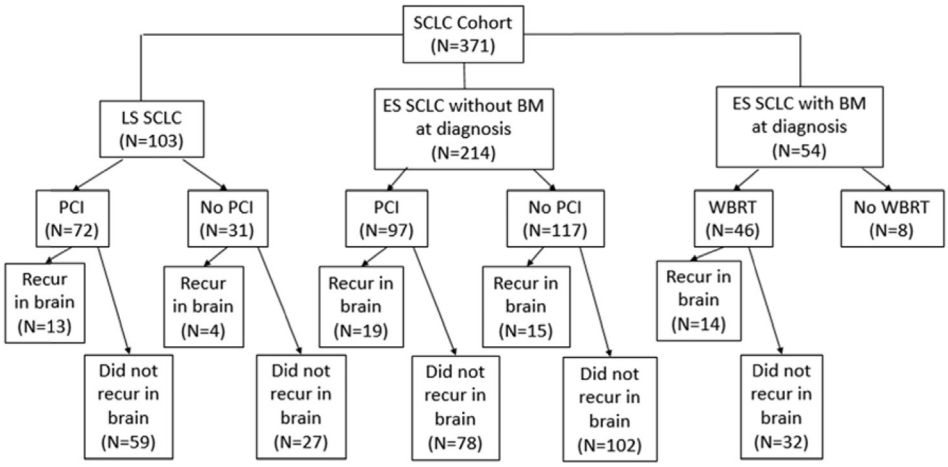
Appendix



Appendix A. Study cohorts. ES, extensive stage; LS, limited stage; PCI, prophylactic cranial irradiation; RT, radiation therapy; SCLC, small cell lung cancer; WBRT, whole brain radiation therapy.

Appendix B
Radiologic Diagnosis of Intracranial Recurrence (n = 65)

Imaging Modality	N (%)
CT without contrast only	8 (12.3%)
CT with contrast only	31 (47.7%)
MRI only	14 (21.5%)
CT without contrast + MRI	0
CT with contrast + MRI	2 (3.1%)
Other*	9 (13.85)
UNK	1 (1.5%)

CT, computed tomography; MRI, magnetic resonance imaging; UNK, unknown.

* MRI without contrast or ct with unknown contrast status.

Appendix C
Multivariate Analysis

	HR (95%CI)	*P* Value
Factor	Death after PCI	
Stage at diagnosis (LS)	3.35 (0.93–12.11)	.07
Interval between brain RT	0.87 (0.81–0.93)	**<.0001**
Extracranial recurrence	1.57 (0.49–5.02)	.45
Factor	In-brain recurrence after PCI	
Stage at diagnosis (LS)	3.56 (1.40–9.04)	**.008**
Extrathoracic disease present	1.03 (0.41–2.59)	.96
Initial cranial RT dose	0.65 (0.43–0.99)	.047
Factor	Death – no brain RT*	
Stage at diagnosis (LS)	3.94 (2.26–6.88)	**<.0001**
Intracranial recurrence	3.26 (1.87–5.66)	<.0001
Factor	In-brain recurrence – no brain RT*	
Stage at diagnosis (LS)	4.30 (1.20–15.4)	**.025**
Factor	Death – BM at diagnosis	
Intracranial recurrence	0.87 (0.37–2.03)	.74
Initial cranial RT dose	0.95 (0.92–0.99)	.014
RT dose at recurrence	0.95 (0.90–1.01)	.10
Extracranial progression	0.42 (0.17–1.00)	.05
Factor	In-brain recurrence – BM at diagnosis	
n/a	n/a	n/a

Bolded *P*-value of <.05 indicates statistical significance.
* Did not have brain metastases at diagnosis (no whole brain radiotherapy) and did not have PCI.

Appendix D
Reirradiation Dose Fractionation and Toxicity

ReRT	N = 30
WBRT dose schedule	
18–20 Gy/10	18 (60.0%)
25 Gy/10	3 (10.0%)
20 Gy/5	3 (10.0%)
20 Gy/8	1 (3.3%)
17.5 Gy/5	1 (3.3%)
12 Gy/5	1 (3.3%)
Stereotactic dose schedule	
30 Gy/5	2 (6.7%)
22.5 Gy/1	1 (3.3%)
Toxicity	
Fatigue	4 (13.3%)
Headache	3 (10.0%)
Nausea +/− vomiting	2 (6.7%)
None	5 (16.7%)
UNK	12 (40.0%)
ECOG following ReRT	
0–2	6 (20.0%)
3–4	7 (23.3%)
UNK	17 (56.7%)

ECOG, Eastern Cooperative Oncology Group performance status; Gy, gray; ReRT, reirradiation; SRS, stereotactic radiosurgery; UNK, unknown; WBRT, whole brain radiation therapy.