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Brain metastases

The incidence of symptomatic brain metastases from extra-pulmonary small cell carcinoma: Is there a role for prophylactic cranial irradiation in a clinically relevant population cohort?

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ABSTRACT

Background and purpose: To examine the incidence and outcomes of patients with brain metastases from extra-pulmonary small cell carcinoma (EPSCC) and assess the indication for prophylactic cranial irradiation (PCI).

Materials and methods: A Provincial cancer registry was used to conduct a retrospective, population-based study of patients diagnosed with EPSCC between January 1997 and December 2011. The primary end point was the incidence of brain metastases. The secondary endpoint was overall survival. A "PCI Eligible" cohort was defined to provide an estimation of the incidence of brain metastases in clinically relevant patients.

Results: In 287 patients, the primary sites were 21% gastrointestinal, 34% genito-urinary, 14% gynecologic, 5% head/neck and 25% unknown primary. Thirty-five (12.5%) patients had brain metastases: 12 (4.2%) at initial diagnosis and 23 (8%) later in the disease course. In PCI Eligible patients, the 3-year cumulative incidence of new brain metastases was 5.5% for M0 stage disease and 26.3% for M1 disease. There was no significant difference in the incidence of brain metastases between primary sites.

Conclusions: The incidence of brain metastases in patients with EPSCC is comparatively low, even in a cohort of patients that were suitable for PCI. Based on our analysis, we cannot recommend PCI for patients with EPSCC.

The large majority of small cell carcinomas originate from the lung and are characterized by poor differentiation, a high proliferation index, and a clinical behavior of aggressive growth and early metastases [1]. Brain metastases are frequent in small cell lung cancer (SCLC), and can be the first site of distant failure. For patients with limited disease (LD) stage SCLC, the 3-year cumulative incidence of brain metastases in patients in remission is estimated at 59% [2]. For these patients, prophylactic cranial irradiation (PCI) has been shown to reduce the risk of brain metastases, improve disease-free survival, and improve overall survival (OS) [2–4]. In a study of extensive disease (ED) stage SCLC, PCI decreased the incidence of symptomatic brain metastases and improved survival in patients with a good response to systemic therapy [5].

Extra-pulmonary small cell carcinoma (EPSCC) is much less common, accounting for <5% of small cell cancers [6]. Gastrointestinal (GI), gynecological (GY), genitourinary (GU), and head and neck (HN) organs are common sites of origin. Despite a similar histology to SCLC, EPSCC has been reported to have a different disease biology and pattern of metastatic spread [7]. However, in the absence of good prospective data, the management of EPSCC, including use of PCI, has often followed that of SCLC [7,8]. The frequency of brain metastases in EPSCC is less well known with most available data from small single-institution studies [8–10].

We examined the incidence and outcomes of patients with brain metastases from EPSCC in a large population to evaluate the role of PCI. In addition, we defined a "PCI Eligible" cohort to provide an estimation of the incidence of brain metastases in clinically relevant patients.

Methods

Using a Provincial cancer registry, a retrospective, population-based cohort of patients diagnosed with EPSCC in British Columbia,

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Canada, between January 1997 and December 2011 was identified. The study inclusion criterion was a pathologic diagnosis of small cell carcinoma in accordance to the definition provided by the World Health Organization [11,12]. The study exclusion criteria were: primary of the lung, trachea, or bronchus, Merkel cell carcinoma of the skin, well-differentiated neuroendocrine tumor, paraganglioma, and small cell sarcomas. Primary sites were categorized into the following tumor groups: GI, GU, HN, GY, and Primary Unknown (PU). For PU, there were no radiographic findings or positive immunohistochemical markers to support a pulmonary origin. The patient's medical records were reviewed for patient characteristics, disease characteristics, systemic therapy use, and clinical outcomes.

Patients were divided into local/locally advanced disease (M0 disease) and metastatic disease (M1 disease) cohorts, according to the American Joint Committee on Cancer for each disease site [13]. The M0 vs. M1 staging draws some parallels to the LD vs. ED classification used in the Veterans Affairs Lung Study Group staging system for SCLC.

The primary endpoint was the incidence of brain metastases. The time to diagnosis of brain metastases was measured from the date of pathologic diagnosis to the date of brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) that demonstrated metastasis. Brain imaging was not part of standard follow-up unless patients were symptomatic. The secondary endpoint was OS. Survival was measured from the time of pathologic diagnosis to death.

We further defined a "PCI Eligible" cohort where PCI is most likely clinically relevant. Inclusions for this cohort were patients with M0 disease who received local or systemic treatment, or M1 disease who responded to systemic treatment. Exclusion criteria were patients with M0 or M1 disease who did not receive any treatment and patients with a performance status of ECOG 3-4. For the purpose of this study, patients with brain metastases at initial diagnosis and patients who received PCI were also excluded from this cohort.

Patient and tumor characteristics were compared across the tumor groups using the Fisher Exact test for categorical variables and the Kruskal–Wallis rank-sum test for continuous variables. A competing risk analysis was used to estimate the cumulative incidence of brain metastases. In our analysis, patient death before developing brain metastases was considered a competing risk event. Patients who had not developed a brain metastasis and had not died were censored at the time of last follow-up. Gray's test was used to test for differences in the cumulative incidence curves between disease stages and primary sites [14]. The association between brain metastases, primary site and patient characteristics was assessed using a proportional sub-distribution hazards model (Fine-Gray model) [15]. The OS was estimated using the Kaplan–Meier method and survival was compared using the log-rank test. The Cox proportional hazards model was used to assess association between OS, primary site, and patient characteristics. For the variables included in the Fine-Gray and Cox models, the proportional hazards assumption was assessed using log-minus-log plots, scaled and weighted Schoenfeld residuals. All reported p-values are two-sided, with a p-value < 0.05 set at the level of significance. For the statistical analysis the R Statistical Language (version 2.1–5; http://cran.r-project.org/) was used [16]. The study was approved by the Research Ethics Board of the British Columbia Cancer Agency.

Results

For the population, 287 consecutive patients were identified with EPSCC. By tumor group there were 60 (21%) GI, 100 (35%) GU, 41 (14%) GY, 14 (5%) HN and 72 (25%) PU (Table 1). One hundred fifty-one (53%) patients had M0 disease and 136 (47%) patients had M1 disease at initial diagnosis. In the PU group, no patients with M0 disease were identified. One hundred nighty-six (68%) patients received chemotherapy as part of management. Patients with M0 disease more frequently received chemotherapy than M1 disease, 79% vs. 57% ($p < 0.001$). Median follow-up time for living patients was 31.6 months.

There were 139 patients in the PCI Eligible cohort after excluding 148 PCI Ineligible patients. The PCI Ineligible group consisted of 12 patients with brain metastases at initial diagnosis, 7 patients who were treated with PCI, 86 with an ECOG 3-4 performance status, 26 patients with stage M1 disease who did not receive systemic treatment or did not respond to systemic treatment, 12 patients with stage M0 disease who did not receive curative intent treatment (8 frail, 1 dementia, 1 refused treatment, 1 not suitable for repeat high dose radiotherapy, 1 died before treatment) and for 5 patients the treatment response could not be evaluated. The PCI Eligible cohort of patients were significantly younger, received more chemotherapy, were diagnosed in an earlier disease stage, presented with a better performance status and lived longer than PCI Ineligible patients (Table 2).

For the population of 287 patients, 35 patients (12.4%) were found to have brain metastases: 12 (4.2%) at initial diagnosis and 23 (8%) later in the disease course, with a 12.5% (CI 8.9–16.6) 3-year cumulative incidence of brain metastases (Table 3). Seven patients (2.4%) received PCI: 4 patients with M0 disease and 3 patients with M1 disease. Two of the patients treated with PCI later developed brain metastases. The small number of patients who received PCI did not lend to a meaningful analysis.

For the PCI Eligible cohort of 139 patients, the 3-year cumulative incidence of brain metastasis was 11.3% (CI 6.6–17.4). There were significantly more brain metastases in the M1 cohort (26.3%; CI 13.3–41.3) in comparison to the M0 cohort (5.5%; CI 2–11.7), $p < 0.001$. The cumulative incidence by disease stage is

Table 1
Extra-pulmonary small cell cancer by primary site.

Primary site	All (n = 287)	By tumor stage	
	No. (%)	M0 (n = 151) No. (%)	M1 (n = 136) No. (%)
GI			
Anal Canal	5 (1.7)	5 (3.3)	0 (0)
Esophagus	23 (8)	11 (7.3)	12 (8.8)
Gall Bladder	2 (0.7)	2 (1.3)	0 (0)
Large Intestine	7 (2.4)	1 (0.7)	6 (4.4)
Pancreas	6 (2.1)	2 (1.3)	4 (2.9)
Rectum	9 (3.1)	3 (2)	6 (4.4)
Stomach	8 (2.8)	5 (3.3)	3 (2.2)
GU			
Bladder	78 (27.2)	61 (40.4)	17 (12.5)
Prostate	19 (6.6)	11 (7.3)	8 (5.9)
Ureter	2 (0.7)	2 (1.3)	0 (0)
Urethra	1 (0.3)	1 (0.7)	0 (0)
GY			
Cervix	24 (8.4)	20 (13.2)	4 (2.9)
Endometrium	2 (0.7)	2 (1.3)	0 (0)
Ovary	12 (4.2)	10 (6.6)	2 (1.5)
Vagina	3 (1)	2 (1.3)	1 (0.7)
HN			
Larynx	2 (0.7)	1 (0.7)	1 (0.7)
Major Salivary Gland	4 (1.4)	4 (2.6)	0 (0)
Nasal Cavity	4 (1.4)	4 (2.6)	0 (0)
Oral Cavity	1 (0.3)	1 (0.7)	0 (0)
Pharynx	3 (1)	3 (2)	0 (0)
PU	72 (25.1)	0 (0)	72 (52.9)

Abbreviations: GI, gastro-intestinal; GU, genito-urinary; HN, head and neck; GY, gynecological; PU, primary unknown.