Should Patients with Extrapulmonary Small-Cell Carcinoma Receive Prophylactic Cranial Irradiation?

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Introduction: Extrapulmonary small-cell carcinoma (EPSCC) is a rare disease. Management is based on small-cell lung carcinoma. Prophylactic cranial irradiation (PCI) is not routinely administered in EPSCC. This study investigates the role of PCI in EPSCC, by analyzing the incidence, treatment, and survival of patients with brain metastases in a national cohort. Disease biology and epidemiology are also investigated.

Methods: Patients diagnosed with primary EPSCC from the National Cancer Registry of Ireland from 1995 to 2007 were identified. The number of patients who developed brain metastases, their survival, and treatment data were documented. Patients who received PCI were investigated. Patient and disease characteristics, treatment, and survival data were stratified by stage and primary site.

Results: Two hundred eighty patients were identified; 141 (50.4%) were men and 139 (49.6%) were women. One hundred eighty six patients (66.4%) had extensive-stage disease, 65 (23.2%) had limited-stage disease, and in 29 patients (10.3%) the stage was unknown. Eighteen patients (6.4%) developed brain metastases, with a median overall survival of 10.1 months. Eleven (61%) received cranial irradiation, and 12 (67%) received palliative chemotherapy. Two patients in the entire cohort (0.17%) received PCI. The most common primary sites included the esophagus (n = 43; 15.4%), cervix uteri (n = 17; 6.0%), bladder (n = 13; 4.6%), and prostate (n = 10; 3.6%). Median overall survival was 15.2 months (10.2–20.6) for limited-stage disease, 2.3 months (1.7–3.1) for extensive-stage EPSCC, and 3.7 months (1.3–8.3) for disease of unknown stage.

Conclusion: Brain metastases were uncommon in EPSCC compared with small-cell lung carcinoma. PCI is thus probably not warranted in this disease.

Key Words: Extrapulmonary small cell, Prophylactic cranial irradiation.

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Small-cell carcinomas (SCLCs) are a subset of neuroendocrine tumors with poor differentiation, elevated mitotic rate, and a high proliferation index.[1] These cancers are biologically aggressive, disseminate early, and have a poor overall prognosis. SCLCs most commonly originate in the lung. Between 10 and 14% of patients with SCLC present with brain metastases at diagnosis, and 80% will develop brain metastases within 2 years of diagnosis.[2] Prophylactic cranial irradiation (PCI) reduces the morbidity and mortality associated with brain metastases in SCLC. Phase III studies demonstrate an improvement in overall survival (OS) and quality of life with PCI in limited-stage (LS) and extensive-stage (ES) SCLC that demonstrate a response to systemic chemotherapy.[3–5]

SCLCs that originate outside of the lung are termed extrapulmonary small-cell carcinomas (EPSCCs). This disease constitutes 0.1% to 0.4% of cancers in the United States per year, and 2.5% to 4% of all SCLCs.[6] Management of EPSCC is modeled on SCLC, as no prospective data exist for this uncommon disease.[7] However, the use of PCI is not routinely recommended. Knowledge of the biology of EPSCC is based on single-institution studies and case series.

This study aims to analyze the incidence, treatment, and survival of patients with brain metastases in a national cohort of EPSCC, and the current use of PCI, thereby investigating the possible role of PCI in this disease. Secondary aims were to assess patient and disease characteristics, treatment, and survival of all patients in one of the largest cohorts in the literature on this disease. These data would provide insights into the biology of EPSCC compared with that of SCLC.

MATERIALS AND METHODS

A national audit was undertaken of patients diagnosed with primary EPSCC from the National Cancer Registry of Ireland (NCRI), between 1995 and 2007. Clinical data collected included: patient age, sex, smoking status, primary site, stage, and grade. Treatment data consisted of the number of patients who underwent surgery, chemotherapy, and radiotherapy (RT), stratified by disease stage. Information on all registered metastatic tumors in these patients was compiled, as far as these data were available. Patients were classified as ES if site(s) of metastasis or stage IV disease was recorded. All other patients were classified as LS.

Chemotherapy was subclassified into postoperative, concurrent/sequential, or palliative. RT was subdivided into local treatment to the primary, local treatment to the metastasis,

whole-brain radiotherapy, and PCI. OS was defined as the time interval from histologic diagnosis to death.

Patients who developed brain metastases were identified, and their clinicopathologic features were analyzed. These included age, primary site, stage, metastatic sites, and OS.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. OS data were estimated by the Kaplan–Meier method, and survival curves were compared with the log-rank method. Cox regressional hazard model was used for univariate analysis to assess the effects of different covariates on OS. Covariates that achieved statistical significance ($p < 0.05$) were entered into a multivariate Cox proportional hazard model to identify independent prognostic factors.

RESULTS

Study Population

Two hundred eighty patients with a confirmed histologic diagnosis of EPSCC were identified. Patient characteristics are summarized in Table 1.

Disease and Treatment Characteristics

Disease characteristics are shown in Table 2. The most common primary sites were the esophagus ($n = 43$; 15.4%), cervix uteri ($n = 17$; 6.0%), bladder ($n = 13$; 4.6%), and prostate ($n = 10$; 3.6%). At diagnosis, 186 patients (66.4%) had ES EPSCC, 65 (23.2%) had LS disease, and in 29 patients (10.3%) the stage was unknown. The most common metastatic sites were the liver ($n = 110$; 34.9%), lymph nodes (LNs) ($n = 58$; 20.7%), lung ($n = 38$; 12.0%), and bone ($n = 36$; 11.4%). Six of 65 patients with LS EPSCC had regional LN involvement.

Treatment

Treatment data are shown in Table 3. One hundred sixteen patients (41.4%) received no form of therapy.

TABLE 1. Patient Characteristics

Patient Characteristic	*n* (%)
Age, yr	
Median	65
Range	17–85
Sex	
Male	141 (50.35)
Female	139 (49.64)
Smoker	
Current	87 (31.07)
Ex-smoker	49 (17.50)
Unknown	58 (20.71)
Never smoker	86 (30.71)

The number of patients with extrapulmonary small-cell carcinoma stratified by age, sex, and smoking status.

TABLE 2. Disease Characteristics

Disease Characteristic	*N* (%)	
Primary site		
Head and neck	12 (4.28)	
Cardiorespiratory		
Thorax NOS	1 (0.3)	
Mediastinum	3 (1.0)	
Trachea	4 (1.4)	
Gastrointestinal		
Esophagus (all)	43 (15.4)	
Stomach	18 (6.4)	
Colon	3 (1.0)	
Rectosigmoid	6 (2.0)	
Other	9 (3.1)	
Hepatobiliary		
Pancreas	3 (1.0)	
Ampulla of Vater	1 (0.3)	
Liver	1 (0.3)	
Genitourinary		
Cervix uteri	17 (6.0)	
Endometrium	3 (1.0)	
Other (genitalia)	6 (1.9)	
Prostate	10 (3.6)	
Bladder	13 (4.6)	
Other (urinary)	6 (2.0)	
Lymph nodes	1 (0.3)	
Unknown	110 (39.2)	
Breast	7 (2.5)	
Skin	3 (1.0)	
Grade		
Well differentiated	1 (0.3)	
Moderately differentiated	5 (1.7)	
Poorly differentiated	68 (24.2)	
Undifferentiated/anaplastic	76 (27.1)	
Unknown	130 (46.4)	
Sites of metastasis	*N* (% of total)	
	Local Recurrence	Distant Metastasis
Total	21	316
Head and neck	2 (9.5)	0 (0)
Cardiorespiratory		
Lung	0 (0)	38 (12.0)
Other	1 (4.8)	9 (2.8)
Gastrointestinal		
Liver	0 (0)	110 (34.8)
Esophagus	3 (14.3)	0 (0)
Peritoneum	1 (4.8)	11 (3.5)
Other	1 (4.8)	12 (3.8)
Genitourinary		
Cervix uteri	5 (23.8)	1 (0.3)
Other (genitalia)	0 (0)	3 (0.9)
Other (urinary)	1 (4.8)	5 (1.6)
Prostate	0 (0)	2 (0.6)
Bladder	3 (14.3)	1 (0.3)

(*Continued*)

TABLE 2. (*Continued*)

Disease Characteristic	*N* (%)	
Lymph nodes	2 (9.5)	58 (18.4)
Skin	0 (0)	7 (2.2)
Bone	0 (0)	36 (11.4)
Connective tissue	0 (0)	2 (0.6)
Brain	0 (0)	18 (5.7)

This table summarizes the number of patients with extrapulmonary small-cell carcinoma stratified by site of primary disease, histopathologic grade, and sites of metastasis, classified as either a local or distant recurrence.
NOS, not otherwise specified.

Fifty-four patients (19.3%) underwent surgery. One hundred fourteen patients (40.7%) underwent chemotherapy. One hundred thirty patients (46.4%) underwent RT. Twenty patients (7%) received concurrent/sequential chemo-radiotherapy.

Survival

Median OS for the entire cohort of patients with LS, ES, and disease of unknown stage was 15.2 months, 2.3 months, and 3.7 months, respectively. Median OS for patients who received at least one modality of treatment was 17.9, 6.6, and 10.7 months for LS, ES, and unknown-stage EPSCC, respectively (Fig. 1).

Two patients in the cohort received PCI. Both were alive at data cutoff, with an OS of 11.1+ months and 33.8+ months, respectively.

Univariate analysis identified disease stage, age, surgery, chemotherapy, RT, and the presence of hepatic or pulmonary metastases as potential prognostic factors. In multivariate analysis, disease stage, surgery, chemotherapy, RT, and the presence of hepatic metastases remained independent prognostic factors (Table 4).

Brain Metastases in EPSCC

Eighteen patients in the cohort (6.4%) developed brain metastases (Fig. 2*B*). Ten patients (56%) were men, and eight (44%) were women. Twelve (67%) were current smokers. Sixteen (89%) of these patients had ES EPSCC at diagnosis, seven of whom had brain metastases at initial presentation. Fourteen patients (77.7%) were diagnosed and recorded as having brain metastases after the year 2000, compared with four patients (22.2%) before 2000. The most common primary site was unknown ($n = 6$; 33%), followed by the esophagus ($n = 3$; 17%), prostate ($n = 3$; 17%), cervix ($n = 1$; 6%), hepatobiliary ($n = 1$; 6%), gastrointestinal tract not otherwise specified ($n = 1$; 6%), stomach ($n = 1$; 6%), ovary ($n = 1$; 6%), and head and neck ($n = 1$; 6%).

In terms of treatment, 16 patients received some form of initial therapy. Two patients (11.1%) underwent surgery, 14 (77.7%) received chemotherapy, of whom 13 (92.9%) were received chemotherapy of palliative intent, and four (22.2%) received RT. All patients with LS EPSCC and regional LN involvement ($n = 6$) received some form of treatment, and none of these patients developed brain metastases. Eleven patients (61%) received whole-brain radiotherapy for the treatment of brain metastases.

The median OS of the 16 patients with brain metastases who received treatment, was 10.5 months, compared with 10.4 months for all treated patients with no evidence of brain metastases (hazard ratio 1.27; 95% CI 0.72–2.35; $p = 0.378$) (Fig. 2). For the two untreated patients with brain metastases, OS was 0.5 and 0.6 months, respectively.

TABLE 3. Treatment Data

	N (% of Total Patients)	Patient No. (% of Treated Patients)		
Treatment Characteristic	**Total**	**Limited Stage**	**Extensive Stage**	**Unknown**
Surgery	54 (19.3)	28 (51.9)	26 (48.1)	1 (1.9)
Chemotherapy				
All	114 (40.7)	36 (31.6)	71 (62.3)	7 (6.1)
Postoperative	17 (6.1)	8 (47.0)	8 (47.0)	1 (5.9)
Concurrent/sequential chemo-radiotherapy	20 (7.1)	12 (60.0)	6 (30.0)	2 (10.0)
Palliative	77 (27.5)	16 (20.8)	57 (74.0)	4 (5.2)
Radiotherapy [a]				
All	130 (46.4)	33 (25.4)	91 (70.0)	6 (4.6)
Local to primary	66 (23.6)	33 (50.0)	27 (40.9)	6 (9.0)
Local to metastasis	44 (15.7)	0 (0)	44 (100)	0 (0)
Whole-brain	11 (3.9)	0 (0)	11 (100)	0 (0)
Unknown	9 (3.2)	0 (0)	9 (100)	0 (0)
Prophylactic cranial irradiation[b]	2 (0.71)	0 (0)	2 (100)	0 (0)

This table indicates the total number of patients with EPSCC who underwent surgery, chemotherapy, radiotherapy, and prophylactic cranial irradiation. Patients are stratified according to stage of disease.
[a]Radiotherapy includes first, second, and third sites of radiotherapy.
[b]Prophylactic cranial irradiation refers to treatment for patients who received brain radiotherapy without documented whole-brain metastases.
EPSCC, extrapulmonary small-cell carcinoma.

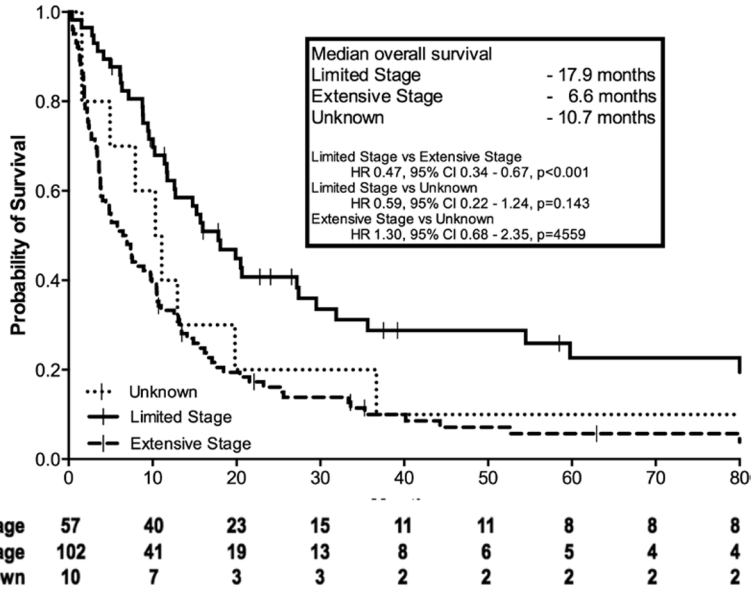

FIGURE 1. Kaplan–Meier plot for overall survival for all treated patients, grouped by disease stage at diagnosis. Comparison of overall survival was performed via log-rank test. HR, hazard ratio; CI, confidence interval.

DISCUSSION

EPSCC is an uncommon malignancy. In the 12-year period during which 280 cases of EPSCC were recorded by the NCRI, 3028 cases of SCLC were recorded. Prospective data on EPSCC would thus be difficult and time consuming to obtain.

To our knowledge, this is the largest data set on EPSCC, which examines the incidence and management of brain metastases. This study demonstrates a low incidence of brain metastases (6.4%) that is comparable with the incidence in published studies (4.1%–13%).[8–10] Two patients in our cohort underwent PCI as part of initial management. Only 2.5% of the entire patient cohort presented with brain metastases at initial diagnosis, a much lower incidence compared with SCLC.[2] This would suggest that the natural history of EPSCC differs from that of SCLC with respect to the development of brain metastases.

The median survival data for both LS and ES EPSCC in this cohort are poor compared with that in published studies[7,8,11] However, 41.4% of our cohort received no treatment at all, and only 40.7% received any chemotherapy. The OS data in this study are derived from a population-based registry with a larger sample size, and is comparable to larger provincewide data.[12] The survival data in this study might therefore represent more realistic outcomes in ESPCC. However, all patients who developed brain metastases received some form of therapy. The low incidence of brain metastases can thus be explained by a lack of receipt of standard therapy by a large proportion of the cohort, resulting in poor OS, and an inability to live long enough to develop brain metastases.

Differences between SCLC and EPSCC in terms of disease biology and pattern of metastatic spread constitute the subject of ongoing debate. In LS SCLC, regional LN involvement is common and is linked to the development of brain metastases.[13]

The LS EPSCC subset in this study demonstrated a low rate of regional LN involvement, and no development of brain metastases. Moreover, 33.3% (n = 6), 27.7% (n = 5), and 5.5% (n = 1) of patients with brain metastases had EPSCC of gastrointestinal, genitourinary, and hepatobiliary origin, respectively. Metastasis of these primary tumor sites to brain occurs in less than 4% of cases, and could also account for the overall low incidence of brain metastases in this cohort.[14]

In terms of diagnosis, most cases of brain metastases in this cohort were diagnosed after the year 2000. We postulate that this could be related to increased access and use of advanced imaging modalities. However, registry records are insufficient to confirm this assertion.

A large proportion of patients in this study underwent surgical treatment for a disease that is classically treated with chemo-radiotherapy or chemotherapy alone. A minority of patients with SCLC would be amenable to surgery. This could suggest a biological difference between SCLC and EPSCC, which impacts optimal management. This is in keeping with a previously published study on EPSCC treatment in the Surveillance Epidemiology and End Results (SEER) database.[15]

It is also noted that in a significant proportion of patients in this cohort, the stage of disease was unknown. The median OS for this group of patients was poor, suggesting the possibility that these cases could have represented unconfirmed ES SCLC.

In terms of the risk factors for EPSCC, 66.7% of the patients (n = 12) who developed brain metastases were current smokers. However, only 31% (n = 87) of the entire cohort represented current smokers, and 20% (n = 58) did not have their smoking status recorded. Possible genomic abnormalities in smokers compared with nonsmokers could account for these findings, and require further study. This is in contrast with SCLC, which is a disease of the smoking population.[16]

TABLE 4. Univariate and Multivariate Analyses of Patient and Treatment Characteristics

	Univariate Analysis			Multivariate Analysis		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Stage						
Limited	1			1		
Extensive	2.81	2.05–3.92	<0.001	1.93	1.36–2.77	0.0002
Unknown	2.45	1.49–3.92	0.0006	1.53	0.91–2.50	0.1064
Sex						
Male	0.95	0.74–1.22	0.6891			
Female						
Smoking						
Current	1					
Ex	0.78	0.54–1.14	0.1997			
Never	1.11	0.80–1.52	0.5403			
Unknown	0.65	0.47–0.93	0.0196			
Age (yr)						
<65	0.61	0.47–0.78	0.0001	0.84	0.51–1.15	0.4538
≥65						
Surgery						
Yes	0.37	0.26–0.51	<0.0001	0.39	0.26–0.58	<0.0001
No						
Chemotherapy						
Yes	0.45	0.35–0.58	<0.0001	0.47	0.34–0.64	<0.0001
No						
Radiotherapy						
Yes	0.43	0.33–0.56	<0.0001	0.5	0.37–0.66	<0.0001
No						
Brain metastases						
Yes	0.88	0.52–1.39	0.5957			
No						
Hepatic metastases						
Yes	2.21	1.70–2.87	<0.0001	1.48	1.10–1.92	0.0088
No						
Pulmonary metastases						
Yes	1.45	1.03–1.99	0.0334	1.38	0.97–1.92	0.0732
No						

This table indicates the hazard ratios, confidence intervals, and *p* values by univariate analysis, for disease stage, sex, smoking status, age, presence of brain, hepatic, and pulmonary metastases. Hazard ratios, confidence intervals, and *p* values by univariate analysis are tabulated for treatment characteristics including surgery, chemotherapy, and radiotherapy. Subsequent multivariate analysis for characteristics with a statistically significant univariate analysis, are included.

The most common sites of disease for EPSCC were the esophagus, cervix, bladder, and prostate. Three of these four sites are hollow visci that are prone to local inflammation, infections, and reflux conditions. No data could be found in the literature regarding possible etiological factors of EPSCC. These observations can thus be considered hypothesis-generating.

This study highlights the importance of a national cancer database, particularly to provide insights into the incidence and behavior of rare cancers. A possible limitation of our study, which applies to all registry-based studies, concerns data completeness. However, the NCRI has a 97% estimation of data completeness for primary registration. Also, in relation to the pathological classification of tumor grade, SCLCs are poorly differentiated or undifferentiated carcinomas. Six patients were classified as well or moderately differentiated, and in 130 cases histologic grade was not recorded. As this data set spans a 12-year period, older data could have been misclassified.

There are currently no guidelines that recommend the routine use of PCI in EPSCC. This is the largest data set aimed at investigating this clinical question. These data do not support PCI in the treatment of EPSCC because of a low incidence of brain metastases and possible fundamental differences in disease biology and metastatic spread between EPSCC and SCLC.

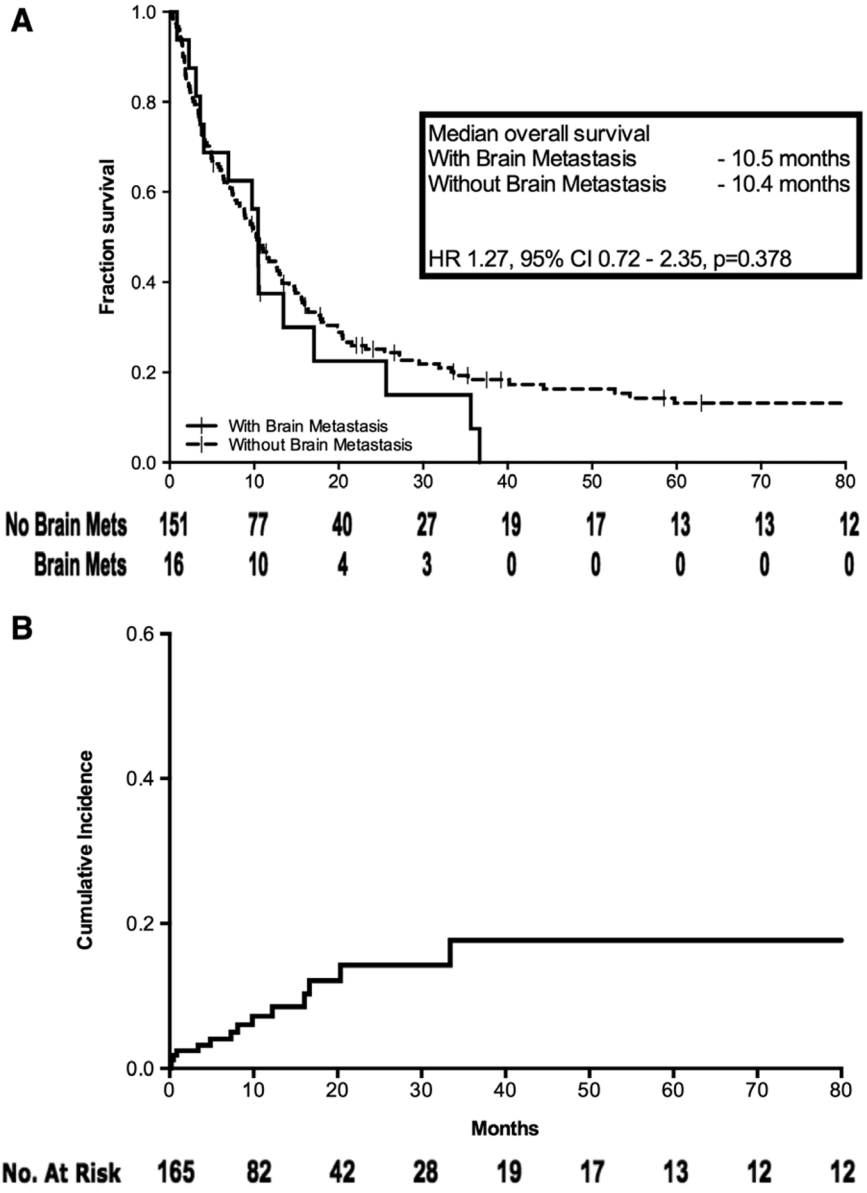

FIGURE 2. *A*, Kaplan–Meier plot for overall survival for all treated patients, grouped by presence versus absence of brain metastases. Comparison of overall survival was performed via log-rank test. *B*, Estimate of cumulative incidence of brain metastases. HR, hazard ratio; CI, confidence interval.

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