Extrapulmonary Small-Cell Carcinoma Compared With Small-Cell Lung Carcinoma

A Retrospective Single-Center Study

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BACKGROUND. The study was conducted with the aim of reviewing the clinical features, therapy, and natural course of patients with extrapulmonary small-cell carcinoma (EPSCC) and small-cell lung carcinoma (SCLC) to better define current concepts regarding EPSCCs.

METHODS. The medical records of patients with proven diagnosis of small-cell carcinoma (SmCC) between January 1999 and May 2006 were retrospectively reviewed. A total of 65 SmCC cases were included in the study (11 [17%] cases of EPSCC and 54 [83%] cases of SCLC).

RESULTS. Progression-free survival of all patients with EPSCC and patients with extensive EPSCC disease was 7 months (95% confidence interval [CI], 0.58–13.42) and 7 months (95% CI, 4.71–13.29), respectively. Overall survival of all patients with EPSCC and patients with extensive EPSSC disease was 32 months (95% CI, 18.74–45.26) and 28 months (95% CI, 12.24–43.76), respectively. Progression-free survival and overall survival for all patients with SCLC were 5 months (95% CI, 2.26–7.74) and 10 months (95% CI, 5.95–14.05), respectively. Progression-free survival and overall survival for patients with extensive disease were 3 months (95% CI, 4.71–13.29) and 5 months (95% CI, 3.33–6.67), respectively. Overall survival was significantly better in all patients with EPSCC and in patients with extensive EPSCC disease compared with all patients with SCLC and patients with extensive SCLC disease ($P = .014$, $P = .004$, respectively). Early death and brain metastasis were observed in a higher number of patients with SCLC compared with EPSCC; however, these results were not statistically significant ($P = .33$ and $P = .076$, respectively). Smoking history was significantly less in the EPSCC group ($P < .0001$).

CONCLUSIONS. EPSCC is usually treated similarly to SCLC. However, this study suggests some differences such as etiology, clinic course, survival, frequency of brain metastases, and early death between these entities. These possible differences may influence the choice of therapeutic approach. ***Cancer* 2007;110:1068–75.** © *2007 American Cancer Society.*

KEYWORDS: extrapulmonary small-cell carcinoma, pulmonary small-cell carcinoma, treatment, prognosis.

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Extrapulmonary small-cell carcinoma (EPSCC) has been increasingly recognized as a clinicopathologic entity with a biological behavior and prognosis distinct from small-cell lung carcinoma (SCLC). Soon after the first description of small-cell carcinoma (SmCC) in the lungs in 1926, the first report of an EPSCC was published by Duguid et al. in 1930.[1] Since then, SmCC has been observed in many locations within the body; the sites cited so far

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include the head and neck, esophagus, stomach, pancreas, gallbladder, uterine cervix, kidney, urinary bladder, and prostate. In contrast to SCLC, which comprises about 20% of all lung cancers, EPSCC is uncommon, with an overall incidence of approximately 0.1% to 0.4% in nonpulmonary sites. One thousand new cases are estimated to occur every year in the US. SmCC arising from extrabronchial sites often represent a diagnostic and therapeutic problem. EPSCC is still somewhat under-recognized or confused with metastatic SCLC.[2] Although there have been a few sporadic reports on EPSCC, much remains to be uncovered about the clinical features, optimal treatment, and natural history. We conducted this study with the aim to review the clinical features, therapy, and natural course of patients with EPSCC and SCLC at our center and to compare them to better define current concepts regarding this disease.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of our patients with proven SmCC diagnosis between January 1999 and May 2006. Sixty-five patients were included in the study. Each patient's medical file included information on age, gender, smoking habit, past medical history, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, primary tumor site, stage, treatment details, and survivals.

The histologic criteria applied for the diagnosis of EPSCC were identical to those for SmCC in the lung.[3] Patients with well-differentiated neuroendocrine tumor, mixed histologic types, and Merkel cell carcinoma of the skin were excluded. EPSCC was defined as having a normal plain radiograph or computed tomography (CT) scan of the chest (in all patients) and normal sputum cytology or negative bronchoscopic findings. Minimal staging procedures for all patients included history and physical examination, chest radiograph, CT of the chest, and/or bronchoscopy, bone scan, and abdominal CT scan. Patients were staged using a 2-stage system. Limited disease was defined as a tumor being localized to the organ of origin and the locoregional lymph nodes, which was easily encompassed within 1 radiation therapy treatment portal, whereas spread of disease beyond locoregional boundaries was considered extensive disease.

Statistical Methods

A complete response required the disappearance of all clinically detectable disease. A partial response required >50% reduction in the sum of the products of 2 largest perpendicular dimensions of bidimensionally measurable lesions. Stable disease was defined as a change of less than 50% reduction or less than 25% increase in the size of 1 or more measurable lesions. All other cases were considered to have progressive disease. An objective response was defined as the sum of complete response and partial response. Overall response was defined as the sum of objective response and stable disease. Progression-free survival was defined as the period from initiation of the first-line treatment to the first evidence of progression or death without progression. Overall survival was defined as the period from initiation of the first-line treatment to death. Early death was defined as the period from the first day of the first-line treatment until the 60th day. The survivals were estimated using the Kaplan-Meier method and comparisons between groups were carried out using the log-rank test. The comparison between the 2 groups on the basis of initial features and response rate as analyzed by chi-square test. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 65 cases of SmCC were included to the study (11 [17%] cases of EPSCC and 54 [83%] cases of SCLC). A total of 11 patients with a diagnosis of EPSCC were identified (Table 1). The patients consisted of 8 (73%) males and 3 (27%) females, with a median age of 56 years (range, 40–73 years). Six patients (55%) had a smoking history of more than 10 pack/years, other patients had no smoking history. The majority of patients (73%) had a relatively good performance status (ECOG, 0–2) at the time of diagnosis. The gastrointestinal (GI) system was the most common primary site, comprising 45% (5 cases; 1 rectum, 2 gallbladders, 2 pancreas) of all EPSCC patients. Three (27%) cases were detected in urinary bladder, 1 case (9%) in cervix. There were 2 (18%) cancer cases with unknown primary origin. Three (27%) patients were classified as limited disease and the remaining 8 (73%) patients as extensive disease at diagnosis. Any of the patients had brain metastasis at the time of diagnosis. No precarcinogenic factors, such as rubber workers, painters, dry cleaners, urachal remnant for urinary bladder and diabetes mellitus, pancreatitis for pancreas, other than smoking were determined. A gallstone history was not observed in the patients with tumors in gallbladder.

Six patients with EPSCC (5 patients with extensive disease whose primary sites were gallbladder, pancreas, urinary bladder, cervix, and unknown primary origin, and 1 patient with limited disease

TABLE 1
Clinicopathological Characteristics and Clinical Course in 11 Patients With EPSCC

No.	Age, y	Sex	Smoker	Primary site	Stage	PS	Treatment	Response	Status	OS, mo
1	40	W	No	Rectum	LD	1	S+4×PE+RT	CR	DOD	68
2	60	M	No	Gallbladder	LD	3	2×P+6×PE+2×top	PR, PR, PR	DOD	28
3	73	W	No	Gallbladder	ED	0	3×PE	PD	DOD	32
4	40	M	Yes	Pancreas	ED	2	2×PE+1×iri	PD, PD	DOD	2
5	56	M	Yes	Pancreas	ED	1	2×P+3×PE	PR, PR	Lost	7*
6	71	M	Yes	Urinary bladder	ED	4	6×CarbE+1×top	PR, PD	DOD	20
7	57	M	No	Urinary bladder	ED	1	3×PE	PR	AWD	3+
8	59	M	Yes	Urinary bladder	LD	1	S+4PE+RT	CR	Lost	7*
9	65	W	No	Cervix	ED	1	3×PE	PR	AWD	3+
10	54	M	Yes	CUP/bone, liver	ED	1	6×PE+1×PE	PR, PD	DOD	9
11	43	M	Yes	CUP/lymph node	ED	1	6×PE	SD	AWD	72+

PS indicates performance status; OS, overall survival in months; W, women; M, men; S, surgery; PE, cisplatin/etoposide; RT, radiotherapy; CR, complete resection; DOD, dead of disease; P, cisplatinum; top, topotecan; PR, partial response; PD, progressive disease; iri, irinitecan; CarbE, carboplatin/etoposide; AWD, alive with disease; CUP, carcinoma of unknown primary.
* Survival is not clearly known due to loss of follow-up.

whose primary site was gallbladder) received a combination of etoposide 120 mg/m^2 intravenously (IV) on 1–3 days and cisplatin 75 mg/m^2 IV (EP regimen) on the first day as the primary chemotherapy. One patient with extensive disease of urinary bladder and an ECOG performance status of 4 received a combination chemotherapy of carboplatin AUC 5 IV and etoposide IV 120 mg/m^2 IV (CE regimen). Case 2 (with extensive disease of gallbladder) and Case 5 (with extensive disease of pancreas) because of hyperbilirubinemia (total/direct bilirubin: 14/7 mg/dL and total/direct bilirubin: 8.3/4 mg/dL, respectively) and poor performance status (each patients' ECOG performance status was 3) received single-agent cisplatin 75 mg/m^2 IV as the primary chemotherapy. After the second cycle of chemotherapy the bilirubin levels of both patients returned to normal and they received the EP regimen. For these patients the overall response rate was 89% (partial response in 6, stable disease in 2), with a median progression-free survival of 7 months.

Two patients with limited disease (1 with rectum and 1 with urinary bladder cancer) underwent radical surgery followed by adjuvant chemotherapy and radiotherapy (Case 1 and Case 8). We did not administer prophylactic cranial irradiation for these patients.

One patient refused second-line chemotherapy and radiotherapy after progression (Case 3). She received only supportive care and died 30 months after progression. Second-line chemotherapy was administered in 3 patients after disease progression. An initial response was only obtained for 1 with gallbladder SmCC (Case 2), but he died from sepsis due to cholangitis after a second cycle of salvage chemotherapy. One patient died because of febrile neutropenia after second-line single agent topotecan regimen (Case 6). The limited disease of the rectum showed a favorable clinical course, with the patient being in disease-free survival with a follow-up of 57 months (Fig. 1). The patient with neurologic symptoms had submitted to another center in the 57th month, and was operated on after a cranial CT showed a single metastasis. The patient was reoperated on in the 62nd month as a result of recurrence in the same location. Both tumors were reported as adenocarcinoma, but no other treatment or examination was made. The patient submitted to our clinic in the 67th month with a complaint of amaurosis in the right eye and vertigo. Multiple metastases were observed in the cranial magnetic resonance imaging (MRI) and he received whole-brain radiotherapy. Previous pathologic samples were reassessed at our center and an SmCC metastasis was observed. In the first month after the radiotherapy he died because of progression of cranial metastases (Case 1). Prolonged survival was observed in 1 patient (Case 11) with SmCC localized in mediastinal and paraaortic lymph nodes, although no primary tumor could be identified (Fig. 2). Stable disease was obtained after 6 cycles EP regimen. No progression was observed for 72 months (Fig. 3) and he is surviving the disease.

During the first-line EP regimen, no early death due to treatment or progression was observed in any patient with EPSCC, despite hyperbilirubinemia (Cases 2, 5), ECOG performance status 3–4 (Cases 2, 6), febrile neutropenia, and renal insufficiency (Cases 3, 6).

Four patients died of disease or unknown cause and 2 patients died of sepsis and febrile neutropenia after second-line chemotherapy.

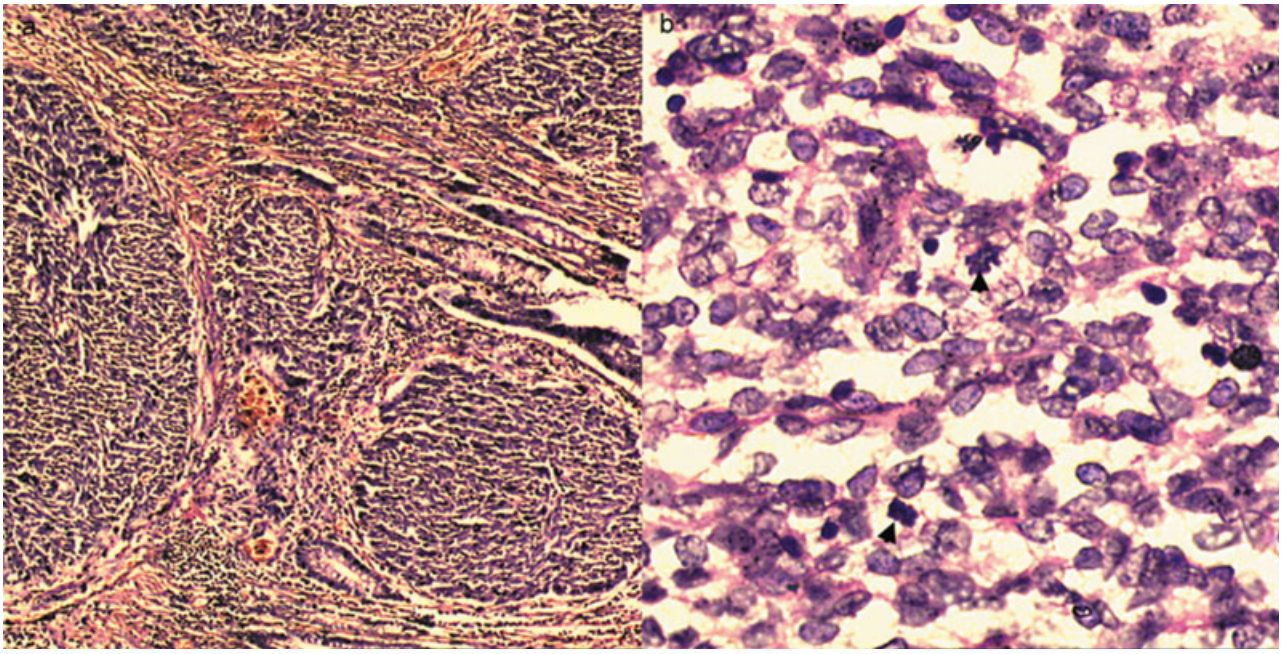


FIGURE 1. (a) Tumor islands, dissecting the epithelium of the rectal mucosa, formed by small cells with scant cytoplasm and atypical hyperchromatic and pleomorphic nuclei (hematoxylin and eosin, ×50). (b) Pleomorphic, hyperchromatic oval-round nuclei of the tumor cells. Note the dispersed chromatin without any prominent nucleoli and atypical mitotic figures (arrowheads) (hematoxylin and eosin, ×400).

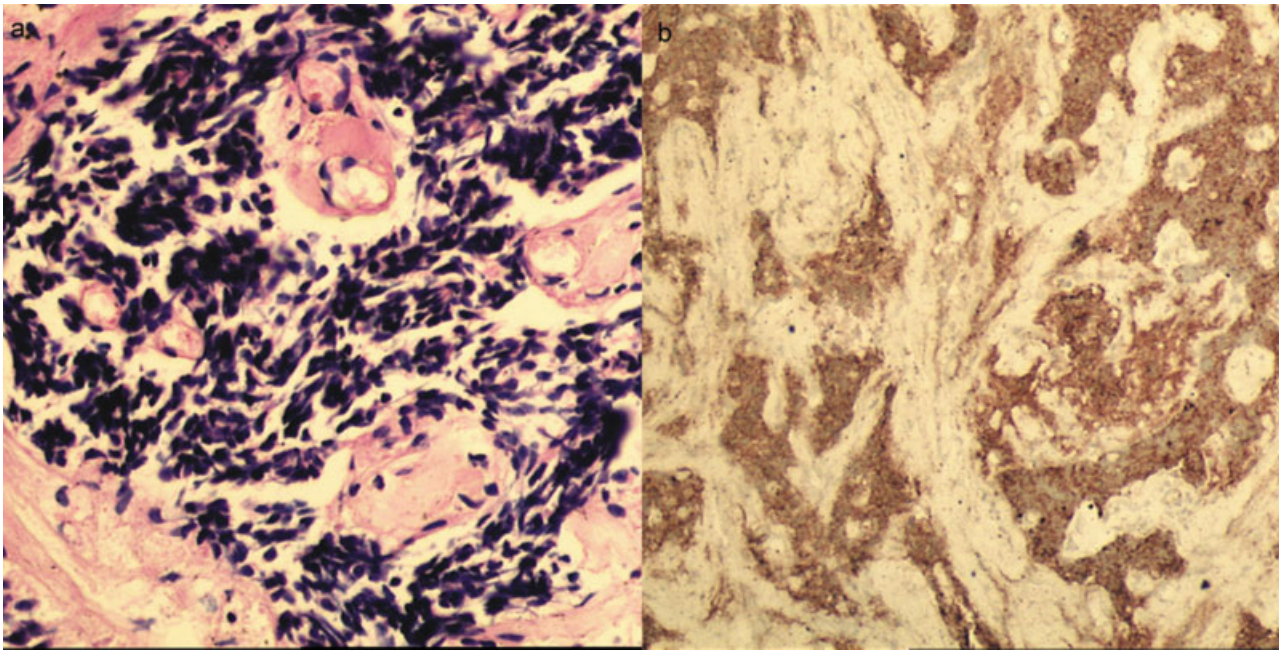


FIGURE 2. (a) Tumor cells haphazardly arranged between fibrous tissue, with scant cytoplasm and round to oval hyperchromatic nuclei. The crashing artifact of the tumor cells is prominent (hematoxylin and eosin, ×200). (b) Diffuse intense staining of the tumor cells for chromogranin-A (×100).

The median follow-up period was 13 (2–72) months. Six (55%) of 11 patients with EPSCC had died of disease at the time of the study analysis, and 3 (27%) patients were still surviving with disease. Two patients (18%) had been lost to follow-up (Cases 5, 8).

Progression-free survival of all patients with EPSCC and patients with extensive EPSCC disease were 7 months (standard error [SE], 3.27; 95% confidence interval [CI], 0.58–13.42) and 7 months (SE, 2.19; 95% CI, 4.71–13.29), respectively. Overall survival of all patients

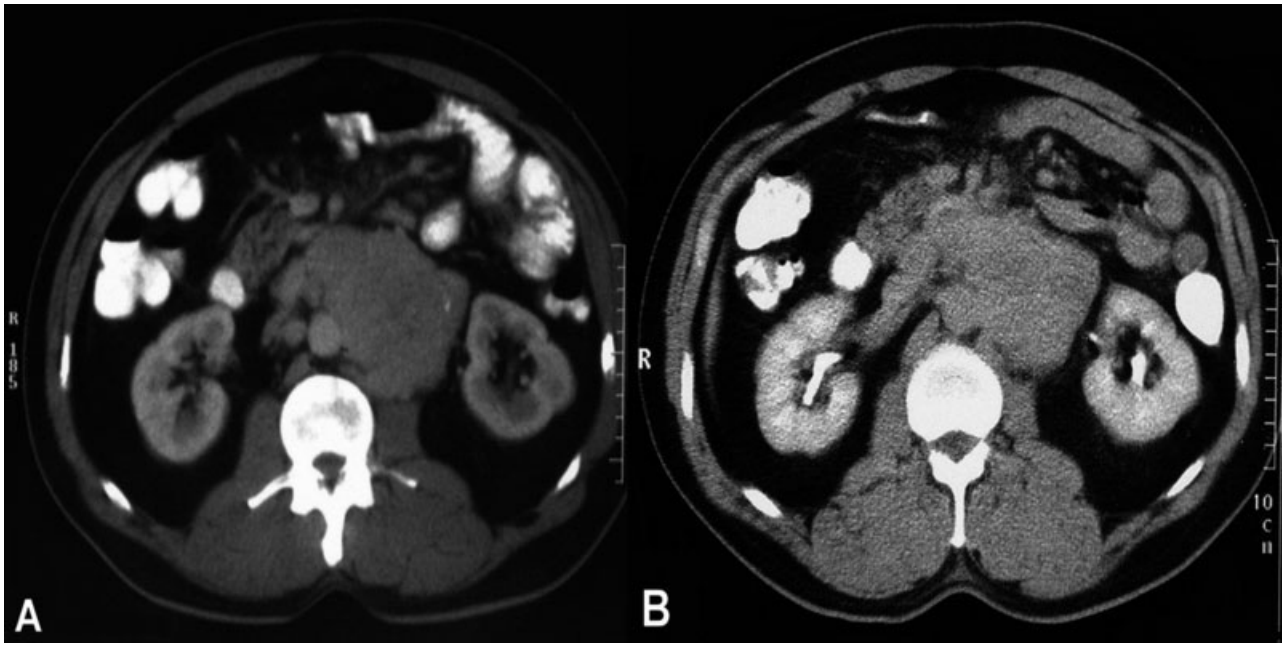


FIGURE 3. (A) Large lobulated soft-tissue lesion measuring 6 × 7 × 15 cm in the paraaortic region is shown. Aorta, left renal artery, vein, and ureter were displaced by the lesion. At some levels invasion of the aorta by the lesion is seen. (B) When compared with computed tomography performed 6 years ago, there was no difference between the 2 tomographic images.

with EPSCC and patients with extensive EPSSC disease were 32 months (SE, 6.77; 95% CI, 18.74–45.26) and 28 months (SE, 1.76; 95% CI, 12, 24–43.76), respectively.

In the SCLC groups the patients consisted of 52 (96%) males and 2 (4%) females, with a median age of 57 years (range, 28–81 years). Fifty-two of 54 (96%) patients had a smoking history. Detailed data were not found about smokers. The majority of patients (81%) had a relatively good performance status (ECOG 0–2) at the time of diagnosis. Twenty-five (46%) and 29 (54%) patients were classified as limited disease and extensive disease, respectively. At the time of diagnosis, 11 patients (38%) had brain metastasis in patients with extensive disease. The median follow-up was 6 (range, 1–27) months.

All patients with SCLC with extensive disease received a combination of EP or CE as the primary chemotherapy. Patients with limited disease received radiotherapy concurrently with the chemotherapy. Prophylactic cranial irradiation for patients in complete response was given. Eight patients died, 4 (50%) because of febrile neutropenia and 4 (50%) because of unexplained causes. Responses were not evaluated in these patients. The overall response rates of 46 patients, whose responses were qualified for evaluation, were 76% (complete response in 10, partial response in 23, stable disease in 2).

Second-line chemotherapy was administered to 10 (19%) patients with SCLC. One patient showed complete response, partial response in 2 patients, and stable in 1 patient. Progressive disease was observed in 1 patient. The responses were not evaluated in 5 patients because of early death.

Progression-free survival and overall survival of patients with the limited disease were 13.5 months (SE, 1.57; 95% CI, 13.4–16.5) and 17 months (SE, 3.03; 95% CI, 11.06–22.94), respectively. Progression-free survival and overall survival for all patients were 5 months (SE, 1.40; 95% CI, 2.26–7.74) and 10 months (SE, 2.06; 95% CI, 5.95–14.05), respectively. Progression-free survival and overall survival for patients with extensive disease were 3 months (SE, 0.6; 95% CI, 4.71–13.29) and 5 months (SE, 0.85; 95% CI, 3.33–6.67), respectively. Overall survival was significantly better in all patients with EPSCC and in patients with extensive disease of EPSCC when compared with all patients with SCLC and patients with extensive SCLC disease ($P = .014$ and $P = .004$, respectively) (Figs. 4, 5). Patients with limited disease could not be compared because of the low number of patients in the EPSCC group. In patients with SCLC, early death was observed in a higher number of patients (9 patients) when compared with EPSCC, but this result was not statistically significant ($P = 0.33$).

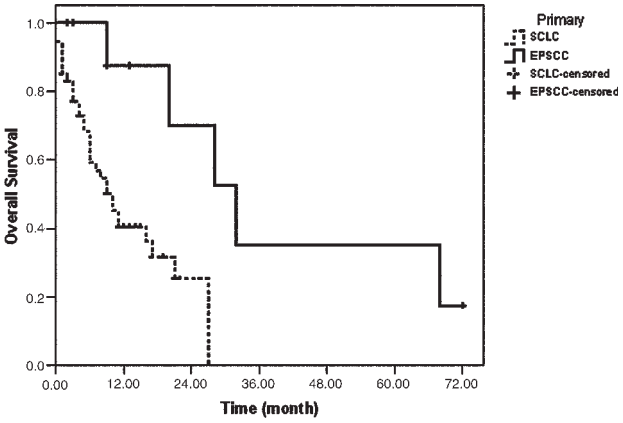


FIGURE 4. Survival curves for all patients with small-cell lung carcinoma and extrapulmonary small-cell carcinoma.

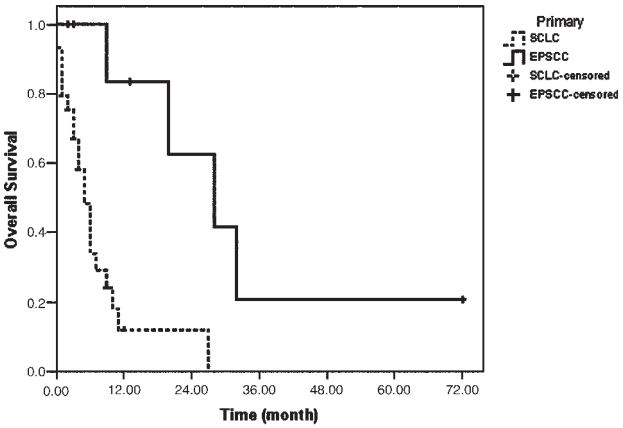


FIGURE 5. Survival curves for patients with extensive stage small-cell carcinoma and extensive stage extrapulmonary small-cell carcinoma.

TABLE 2
Patient Characteristics Between EPSCC and SCLC

Characteristic	EPSCC No. (%)	SCLC No. (%)	*P*
No. of patients	11 (17)	54 (83)	—
Median age, y, [range]	56 [40–73]	57 [28–81]	.87
Sex			.031
Men	8 (73)	52 (96)	—
Women	3 (27)	2 (4)	—
PS (ECOG)			1
0–2	9 (82)	42 (78)	—
3–4	2 (18)	12 (22)	—
Smoker	6 (55)	52 (96)	.000*†
Stage			.326
Limited	3 (27)	25 (46)	—
Extensive	8 (73)	29 (54)	—
Brain metastasis at diagnosis	0 (0)	11 (20)	.076
Response in patients with ED			—
PD	1	9	
OR [SD+ObjR]	8 [2+6], (89)	14 [1+13], (64)	.76
ObjR [PR+CR]	6 [6+0], (67)	13 [13+0], (60)	.672
Response in all patients*			—
PD	1	11	—
OR [SD+ObjR]	10 [2+8], (91)	35 [2+33], (76)	.43
ObjR [PR+CR]	8 [6+2], (73)	33 [23+10], (72)	1
All patients PFS, mo	7	5	.13
All patients OS, mo	32	10	.017†
Patents with ED PFS, mo	7	3	.066
Patents with ED OS, mo	28	5	.0012†
Early death	0	9	.33

EPSCC indicates extrapulmonary small-cell carcinoma; SCLC, small-cell lung carcinoma; PS, performance status; ECOG, Eastern Cooperative Oncology Group; ED, extensive disease; PD, progressive disease; OR, overall response; SD, stable disease; ObjR, objective response; PR, partial response; CR, complete response; PFS, progression-free survival; OS, overall survival.

* Also includes patients who received complete surgery in the group of EPSCC and patients who received chemoradiotherapy in the group of SCLC.

† Significant.

Comparative clinical and demographic features and treatment results of both groups are presented in Table 2. No significant differences were observed between the 2 groups concerning initial hemoglobin, leukocyte, alkaline phosphatase, and lactate dehydrogenase albumin levels (Table 3).

DISCUSSION

The histogenesis of SmCC is controversial and remains speculative.[4] In the light of its rarity and the finding that it has previously been studied from an organ-centered perspective, the overall data regarding EPSCCs are scarce, and its clinicopathologic characteristics are far from being well established. Early data have indicated that EPSCCs share many features of SCLC, including histologic appearance, aggressive clinical behavior, and frequent, yet almost invariably short-lasting, response to either chemotherapy or radiotherapy.[1,4] However, there is no comparative prospective and retrospective study on this type of cancers—of which the etiology and histogenesis remain unknown—showing whether they act in different ways according to their primary location. The discovery of differences and similarities will lead to appropriate treatment methods with respect to the location of origin. But this is rather difficult because of the rarity of this type of cancer. We have at least conducted a retrospective study on all the EPSCC and SCLC patients in our center and compared them with regard to clinical progression and treatment results.

There is no standard treatment for limited disease EPSCC. There is some evidence that surgical resection of limited disease SmCC of the GI, urinary bladder, and cervix can result in long-term disease-free survival.[5–7] In recent years, surgery, if done, was usually performed after induction chemotherapy or

TABLE 3
Laboratory Tests Between EPSCC and SCLC

Variable	Level	No. of patients with EPSCC	No. of patients with SCLC	*P*
Hemoglobin, g/dL, range, 12–16	<10	1	4	NS
	>10	10	47	
Leukocyte/mm^3, range,	<10.000	3	19	NS
4.000–10.000	>10.000	8	35	
Alkaline phosphatase,	<126	6	33	NS
IU/L, range, <126	>126	5	21	
Lactate dehydrogenase,	<450	7	36	NS
IU/L, range, <450	>450	4	19	
Albumin, g/dL, range, 3.5–5	<4	9	43	NS
	>4	2	11	

EPSCC indicates extrapulmonary small-cell carcinoma; SCLC, small-cell lung carcinoma; NS, not significant.

chemoradiotherapy. Nonetheless, most patients being treated with surgery alone have rapid systemic recurrence.[5,8–10] The available data outline several clinical situations for which radiotherapy may be of benefit. Radiation frequently induces clinical response, but a complete response is rare. Whereas local control is usually preserved, disseminated disease appears rapidly in almost all patients. Combined chemoradiotherapy, concurrently or sequentially, results in an occasional pathologic complete response, as well as occasional long-term survivors.[9,11,12] Whereas the use of chemotherapy in extensive disease seems well established, its role in limited disease is less clear. Because of the high risk of micrometastases, some authors have suggested that chemotherapy always be part of treatment. This approach is supported by reports of occasional long-term survival with chemotherapy alone. Others, however, have argued that because long-term survival was usually restricted to patients who received local therapy, chemotherapy has only a minor impact, if any, on the course of limited disease.[5–9,13] Altogether, information on multimodality treatment for limited disease is limited and heterogeneous; surgery was combined, in several sequences, with different chemotherapy regimens, occasionally with radiotherapy. In the absence of clinical trials, the individual contribution of each component to the overall treatment effect cannot be determined. In our study 2 patients with limited disease SmCC of the rectum and the urinary bladder had undergone radical surgery followed by adjuvant chemotherapy and radiotherapy. They showed a relatively favorable clinical course.

For the patients with extensive EPSCC disease, chemotherapy became the mainstay of treatment and it was found to be strongly associated with improved survival. The response to chemotherapy is usually of very short duration. Disease progression after first-line chemotherapy is often characterized by an aggressive course and responses to second-line chemotherapy are rare.[2,5,9–14]

In our study the responses of both the SCLC and EPSCC groups to chemotherapy were similar to and in accordance with the literature. However, if compared with all patients and the patients with extensive disease, the progression-free and general survival results were found to be better in patients with EPSCC. The general survival results were statistically meaningful. Patients with limited disease could not be compared because of the low number of patients in the EPSCC group. Although there is no comparative study in literature, the results concerning patients with extensive EPSCC are frequently similar to SCLC, differing from our results.[9–15] This may be because of the low number of our patients. However, interestingly, prolonged survival was observed in 3 patients with a SmCC of the rectum after the development of brain metastasis, an SmCC localized in gallbladder and an SmCC localized in the lymph nodes, although no primary tumor (Cases 1, 3, and 11) could be identified. These 3 cases with different origins lead us to think that EPSCCs may have a slower progression than SCLCs. Long-term survival in patients with lymph node metastases from SmCC of unknown primary origin has previously been reported in many studies.[9,14–16] This may be because of the finding that these patients constitute a favorable subset among the patients with EPSCCs.

Chemotherapy for EPSCC usually followed that used in SCLC. Cisplatin, etoposide, cyclophosphamide, and doxorubicin represent the backbone of most of the combinations used. The overall response rate in extensive disease, using cisplatin-based or cyclophosphamide/doxorubicin with vincristine or etoposide chemotherapy, is 70% to 90%.[2,5,9–14] We used EP or CE regimens in both groups and in all patients. Although our results are retrospective, these are the first comparative homogenous data in the literature. In addition, our 2 patients with high levels of bilirubin were treated effectively with just platinums. If the response rate (30%–80%) of SCLC to single-agent platinums is taken into consideration, then single-agent platinum is a good treatment option in these patients.[17]

Whereas approximately 2.5% of SmCC occurs in extrapulmonary sites,[2] the same rate was 17% in our series. This is associated with the finding that patients with EPSCC were only treated in our center,

whereas patients with SCLC were also treated by a pulmonologist in 2 others centers in our city.

Brain metastases in patients with EPSCC are rarer than in SCLC.[5,7,12] In our study, brain metastasis observed at diagnosis and follow-up was significantly low in the EPSCC group. In the absence of neurologic symptoms, brain CT is not routinely performed. Because prophylactic cranial irradiation is associated with significant morbidity and information regarding its efficacy in EPSCC is absent, the data are insufficient to routinely give prophylactic cranial irradiation.[2,5,7,9,11,12]

There is no standard stage system for EPSCC. If therapy follows the principles of SCLC (very rare use of surgery), using the Veterans' Administration Lung Study Group system is probably advisable. Although the patients with EPSCC in such sites as urinary bladder or cervix at stages I, II and III are evaluated as limited-disease stages, the prognosis for these patients is different.[6–8] Information provided by the TNM system may be more valuable; there is no consensus about the issue.

In our study smoking history was significantly less in the EPSCC group. Although there is no clear evidence in the literature, smoking habits are rather low in patients with EPSCC. Although SmCC of the gallbladder is usually associated with cholelithiasis, there was no cholelithiasis in 2 patients with SmCC of the gallbladder.[18] It is currently almost impossible to identify, with reasonable confidence, risk factors for EPSCCs; the few attempts to perform risk factor analysis were negative. EPSCCs seem to develop in a similar predisposing background as non-SmCC in the primary site.[5]

In our study the rate of men was significantly higher in the SCLC group. This is associated with the finding that smoking is significantly higher in men in this age group.[19]

Interestingly, early death due to progression or treatment was observed in 9 patients in the SCLC group, whereas no early death of a patient with EPSCC occurred despite comorbid conditions and bad performance status. The reason for these early deaths may be the finding that the lungs, being vital organs—which are usually normal in patients with EPSCC—cannot deal with problems such as others treatments, febrile neutropenia, pneumonia, anemia, and renal insufficiency in patients in an already bad condition. Furthermore, the finding that no early death had occurred because of the progression of EPSCC in our case contributed to this result.

Although the results of our study seem to show that EPSCCs can have different features and clinical progression from SCLC, they cannot constitute clear evidence because of the low number of patients and the heterogeneity and retrospective status of the group. However, several sporadic retrospective studies and case reports show, as our study does, that EPSCCs with different origins have a different clinical progression and prognosis.[5–16]

In conclusion, the data collected in the literature and our study suggest some differences such as etiology, molecular patterns, clinical course, and frequency of brain metastases and higher percentage of long-term survivors after surgical resection between these entities. This possible difference may influence the choice of therapeutic approach. Because crucial differences between these tumors may exist, their management may also eventually diverge. Because prospective clinical studies are unlikely in EPSCC, information from large retrospective series from referral centers, with correlative data, is imperative. Such studies may disclose important aspects of the disease, such as its pathogenesis, its genotypic and phenotypic overlap with pulmonary SmCC, the prognostic and predictive factors, and more.

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