Acta Oncologica, 2007; 46: 846–851

informa
healthcare

ORIGINAL ARTICLE

Extrapulmonary small cell carcinoma: Single center experience with 61 patients

SUNG SOOK LEE[1], JAE-LYUN LEE[1], MIN-HEE RYU[1], HEUNG MOON CHANG[1], TAE WON KIM[1], WOO KUN KIM[1], JUNG SHIN LEE[1], SE-JIN JANG[2], SHIN KWANG KHANG[2] & YOON-KOO KANG[1]

[1]*Division of Oncology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, and* [2]*Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

Abstract

Extrapulmonary small-cell carcinoma (EPSCC) is a clinicopathological entity distinct from small-cell carcinoma (SCC) of the lung. The aim of this study was to review the clinico-pathologic features, treatment modalities, and factors prognostic for survival in patients with EPSCC. We retrospectively reviewed the medical records of patients with EPSCC diagnosed between January 1995 and July 2004 at the Asan Medical Center. We identified 61 patients with EPSCC, 37 with limited disease (LD) and 24 with extensive disease (ED). The most common primary sites were the gastrointestinal (GI) tract (56%) and uterine cervix (18%). Overall survival (OS) at 1 and 3 years was 59% and 29%, respectively, with a median survival of 16 months (range, 1 ~56 months). Treatment information was available for 51 patients, 34 with LD and 17 with ED. Of the 34 LD patients, 25 underwent surgery. Surgery was the only treatment modality in five patients, two of whom remained alive and disease free at last follow-up, 27 and 47 months after surgery, respectively. Adjuvant chemoradiotherapy was administered to 11 patients, nine of whom (82%) had distant failure with a median overall survival of 23 months. Of the eight patients who received adjuvant chemotherapy, four (50%) had distant failure, with a median survival of 21.7 months. In univariate analysis, advanced disease status, as measured by VALSG (LD vs. ED) stage, was a significant prognostic factor for OS ($p < 0.001$). Interestingly, there were no statistically significant differences in progression-free survival or OS between patients with pure ($n = 45$) and mixed ($n = 16$) EPSCC. Overall, the response to various treatment modalities and the median survival time observed were discouraging. Patients with GI primary tumors had poorer prognoses than those with primary tumors at other locations. Fifty six percent of patients with a GI primary tumor had ED at the time of diagnosis, whereas 100% of patients with SCC of the uterine cervix had LD at the time of diagnosis and showed a favorable clinical course. The majority of patients with LD SCC who underwent surgery, followed by adjuvant chemotherapy or chemoradiotherapy, showed tumor recurrence and/or systemic metastases. Clinical trials are needed to define adequate treatment strategies for EPSCC.

Since the first description of extrapulmonary small-cell carcinoma (EPSCC) in 1930, it has been increasingly recognized as a clinical pathologic entity distinct from pulmonary small-cell carcinoma (PSCC) [1–3]. The primary site of EPSCC can be in a variety of organs [4–9] and the clinical course of these tumors has been found to be aggressive, with early dissemination and frequent recurrence [10,11]. Although there have been several sporadic case reports and reviews of case series, much remains to be learned about EPSCC, including its clinical features, optimal therapy and natural history. The aim of this study was to review the clinico-pathologic features, treatment modalities, and prognostic factors for survival in patients with EPSCC.

Patients and methods

We retrospectively reviewed the medical records of the patients with SCC diagnosed or treated between January 1995 and June 2004 at the Asan Medical Center. Of the 947 patients with SCC identified in the pathology registers, 61 had EPSCC. For inclusion, patients were required to have a normal chest radiograph, computed tomography scan of the chest, sputum cytology, and/or negative bronchoscopy.

Correspondence: Yoon-Koo Kang, Section of Oncology, Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-gong, Songpa-ku, Seoul, South Korea 138-736. Tel: +82 2 3010 3230. Fax: +82 2 3010 6961. E-mail: ykkang@amc.seoul.kr

(Received 26 March 2006; accepted 17 October 2006)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860601071893

Patients with well differentiated neuroendocrine tumors, and those with Merkel cell carcinoma of the skin, were excluded.

The following data were collected for each patient: age, gender, ECOG performance status, anatomic location (GI: gastrointestinal; GU: genitourinary; ENT: ear, nose and throat; GY: internal genitalia, Others: bone, retroperitoneal mass) [3], histologic component, sites of metastases at presentation, and extent of disease. The histologic criteria were similar to those for pulmonary neoplasms, namely, round to spindle-shaped small cells with dense nuclei, inconspicuous nucleoli, and sparse cytoplasm. Diagnoses were confirmed immunohistochemically, using antibodies to chromogranin A, synaptophysin and neuron specific enolase (NSE). Mixed SCC was defined as tumors containing both SCC and non-SCC components, regardless of the proportion of the latter [12].

In the absence of an established staging system for EPSCC [13], tumors were staged according to the Veterans' Administration Lung Study Group (VALSG) staging system for primary SCC of the lung [14]. This latter staging system consists of two categories: limited disease (LD), defined as a tumor contained within a localized anatomic region, with or without regional lymph node involvement; and extensive disease (ED), defined as a tumor outside locoregional boundaries [15].

Statistics

Survival was estimated as a function of time from diagnosis to death or latest follow-up using the Kaplan-Meier method [16]. Factors associated with survival were assessed by the log-rank test [17].

Results

Patients and tumors

A total of 61 patients with EPSCC, constituting 6.4% of patients with SCC, were seen at the cancer center of Asan Medical Center between January 1995 to June 2004. Their clinical characteristics at presentation are outlined in Table I. Of the 61 patients, 31 were men and 30 were women; their median age at diagnosis was 67 years (range, 16 – 79 years). Thirty seven patients had LD and 24 had ED. Of the anatomic sites of primary tumors, gallbladder was the most frequent (23%), followed by uterine cervix (18%), and esophagus (11%). The primary sites of ED EPSCC were the GI tract in 19 patients, the GU system in two patients, and other sites in three patients (Table II).

Treatment

Treatment information was available for 51 patients, 34 with LD and 17 with ED. The primary treatment approach for LD varied; surgery, chemotherapy and radiotherapy were all used, either alone or as part of a combined modality treatment scheme tailored to the needs of the patient. In contrast, in 12 of the 17 patients with ED, primary treatment consisted exclusively of chemotherapy.

Treatment of patients with LD

Of the 34 patients with LD, 25 underwent surgery. Primary tumors were located in the GI tract in eight patients, in the ENT in four patients, in the GU tract in three patients, and in the cervix in ten patients. Sixteen of these patients (74%) relapsed, with a median disease free survival of ten months (range, 2.6–52 months) and median overall survival of 17 months.

Surgery was the only treatment modality in five patients, two of whom (one with a rectal primary, and one with a stomach primary) remained alive and disease free for 27+ months and 47+ months, respectively, after surgery. The other three patients relapsed, however, with a median disease-free survival of 10 months. Adjuvant chemoradiotherapy (CRT) was used in 11 of the 25 patients (1 with a GI tumor, 3 with ENT tumors, 1 with a GU tumor, and 6 with GY tumors), and their median overall survival was 23 months. Distant recurrences were observed in nine of these patients (81%), one with a primary tumor in the GI tract, three in the ENT, one in the GU tract and four in the GY. One patient, with a primary cervical tumor, remained alive and disease free at least 4 years after the initial surgery. One patient died without further evaluation.

Platinum-based adjuvant chemotherapy (CT) was administered to eight of the 25 patients, three each with primary tumors in the GI tract and cervix and one each with a primary tumor in the GU and ovary. Median overall survival was 21.7 months in these eight patients. Distant recurrences were observed in four patients (50%), two with primary tumors in the GI tract and one each with a primary tumor in the ovary and cervix. Four patients (1 with a stomach cancer; 2 with cervical cancers; and 1 with a bladder cancer) remained alive and disease free at least 7, 11, 15, and 23 months, respectively, after the initial surgery.

Chemoradiotherapy was the primary treatment in six patients, three with primary tumors of the esophagus, and one each with a primary tumor of the pancreas, cervix, and bone. These six patients relapsed, with a median disease free survival of 9 months (range, 2–33 months); three remain alive,

Table I. Patient characteristics (n = 61).

	Number	Valid%
Age (Years)		
Median (range)	67 (16–79)	
Sex		
Male	31	51%
Female	30	49%
ECOG		
I	42	70%
II	15	25%
III	3	5%
Anatomic location		
GI tract (n = 34)	Esophagus (7), stomach (3), duodenum (1), liver (2), gallbladder (14), pancreas (1), common bile duct (1), rectum (3), colon (2)	56%
GU system (n = 6)	Prostate (3), bladder (3)	10%
ENT (n = 5)	Larynx (3), hypopharynx (1), mouth floor (1),	8%
GY (n = 12)	Cervix (11), ovary (1)	20%
Others (n = 4)	Bone (2), retroperitioneal mass (2)	6%
Other histologic components		
Pure SCC	45	74%
Adeno ca.	6	10%
Squamous cell ca.	7	11%
Transitional ca.	1	1.6%
Urothelial ca.	1	1.6%
Desmoplastic background	1	1.6%
Sites of metastases at presentation		
Liver	16	57%
Peritoneum	6	21%
Bone	3	11%
Gallbladder	1	4%
Cervical LN	2	7%
No. of metastatic sites		
0	37	61%
1	20	33%
2	3	5%
3	1	1%
Stage		
Limited	37	61%
Extensive	24	39%

GI: gastrointestinal tract; GU: genitourinary system; ENT: ear, nose and throat; GY: internal genitalia.

with evidence of disease, 18, 35, and 39 months after diagnosis.

Treatment of patients with ED

Palliative chemotherapy was administered to 17 patients with ED. Of the 15 who received platinum-based chemotherapy, five (33%) responded, one (7%) with a complete response (CR) and four (27%) with a partial response (PR), with a median response duration in the latter of 2.5 months. Two of the 15 patients (13%) remained stable, with a median duration of 1.5 months, and six (40%) showed disease progression. One of the remaining two patients received a doxorubicin-based regimen and the other received an FU-based regimen, and both showed disease progression.

Patients with ED EPSCC who received systemic chemotherapy had a survival advantage compared with those treated with supportive care alone, in that

Table II. The proportion of patients in each anatomic group with LD and ED.

	LD	ED
Anatomic location		
GI tract (n = 34)	15 (44%)	19 (56%)
GU system (n = 6)	4 (67%)	2 (33%)
ENT (n = 5)	5 (100%)	0 (0%)
GY (n = 12)	12 (100%)	0 (0%)
Others (n = 4)	1 (25%)	3 (75%)

their median overall survival was 6 months (range, 1 ~25 months) vs 3 months (range, 1 ~5 months, p =0.03).

Interestingly, the pathology of the relapsed tumors after systemic chemotherapy differed from that of the primary tumor, with a major component being non-SCC. Thus, even during a complete clinical response to chemotherapy, the recurrent tumor may frequently consist of non-SCC clones. Following platinum based chemotherapy in a patient with a primary esophageal small cell cancer, there was a relapse to the squamous cell phenotype. The current chemotherapeutic agents, however, almost invariably failed to completely eliminate adenocarcinoma or squamous cells.

Survival outcomes and prognostic factors

Overall survival at 1 and 3 years was 59% and 29%, respectively, and median survival was 16 months (range, 1 ~56 months). Median survival was 23 months for patients with LD compared with 6 months for patients with ED (p <0.001, Figure 1).

The results of a univariate analysis of various patient and tumor variables are shown in Table III. Several factors were found to correlate with patient outcome, including age, gender, performance status, anatomic location, and extent of disease (LD vs ED). The extent of disease also had an impact on survival.

SCC of the uterine cervix and GU system showed a relatively favorable clinical course. All patients with SCC of the uterine cervix had LD at the time of diagnosis, with a median overall survival of 23 months. In contrast, patients with SCC of the GI tract showed an aggressive clinical course, with median overall survival of 10 months, 56% of these patients had ED at the time of the diagnosis. EPSCC of the gallbladder was an especially fatal disease.

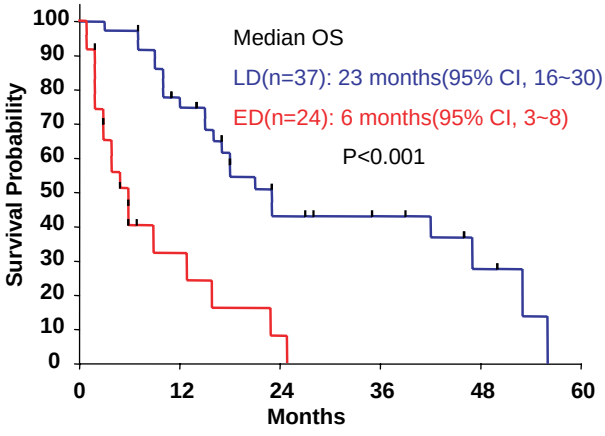

Figure 1. Survival curves relative to extent of extrapulmonary small cell carcinoma at diagnosis (n =61).

Table III. Univariate analysis of survival based on clinical and pathologic factors.

	Median survival, months (CI 95%)	p-value
Age (years)		
<65 (n =46)	18 (1–53)	0.69
≥65 (n =15)	16 (2–56)	
Gender		
Male (n =31)	16 (1–56)	0.814
Female (n =30)	18 (1–53)	
Anatomic Location		
GI (n =34)	10 (1–56)	0.113
Non GI (n =27)	23 (2–53)	
Extent		
Limited (n =37)	23 (3–56)	<0.001
Extensive (n =24)	6 (1–25)	
Histologic component		
Pure SCC (n =45)	15 (7–22)	0.80
Mixed SCC (n =16)	18 (15–20)	

Small cell carcinoma of the gallbladder at presentation metastasizes to the liver (86%), peritoneum (28%), and bone (7%). Survival was very poor, with a median survival of 4 months (range 1.5 ~17.5 months). One patient had mixed small cell carcinoma and adenocarcinoma, and 13 patients had pure small cell carcinoma. Patients with GI primary tumors had a poorer prognosis than those with primary tumors at other locations (Figure 2). However, 56% of patients with a GI primary tumor had ED at the time of diagnosis, whereas 100% of patients with SCC of the uterine cervix had LD at the time of diagnosis and showed a favorable clinical course.

We found that 16 of the tumors had mixed histology, which may influence treatment options. Even in patients showing a complete clinical re-

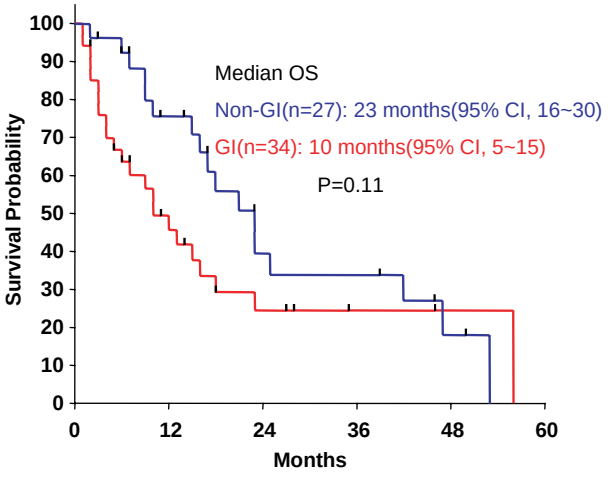

Figure 2. Survival curves for patients with extrapulmonary small cell carcinoma relative to anatomic location GI (n=34) and non-GI (n=27).

sponse to chemotherapy, recurrent tumors will frequently consist of non-SCC clones. However, patients with pure (n = 45) and mixed (n = 16) SCC did not differ significantly in progression-free survival (7 months vs 10 months, p = 0.89) or overall survival (15 months vs 18 months, p = 0.80).

Discussion

Since the first report on an EPSCC in the mediastinal gland [18], this histological subtype has been recognized at all sites of the body except the central nervous system. To date, however, there have been no prospective studies of EPSCC or consensus on adequate treatment strategies. Rather, clinicians usually adopt the treatment algorithm used for PSCC.

Our epidemiologic analysis suggests that EPSCC at sites other than the cervix mainly affects patients of middle age or older, with greater than 70% of these patients being older than age 50 years. If cervix and gallbladder SCC are excluded, EPSCC at most sites was more common in men than in women.

Several anecdotal reports have suggested that long-term disease free survival could be achieved by surgery alone in a subset of patients with LD EPSCC. Indeed, we found that two of the 5 LD EPSCC patients who underwent surgery alone have enjoyed long-term disease free survival. Most patients treated with surgery alone, however, have rapid systemic recurrence [19–22]. Since surgery alone was the single most powerful predictor of poor survival, it is now commonly used as part of multimodal treatment [23].

The available data on adjuvant treatment after surgery for LD EPSCC are limited. The innate radiosensitivity of SCC has led to the use of adjuvant radiotherapy combined with chemotherapy. In patients with PSCC, several randomized trials and two meta-analyses have shown improved survival for combined CRT versus CT alone [24,26].

In our group of patients, it was difficult to determine the best therapeutic option for treatment of LD, primarily because LD is a heterogeneous disease entity with a low incidence rate. Our results indicate, however, that LD EPSCC is characterized by a high rate of systemic recurrence, and that distant metastases are the main cause of death in our series. Although adjuvant chemoradiotherapy was used in 11 of 25 patients, nine of these 11 patients had distant failures, with a median overall survival of 23 months. In the eight patients who received adjuvant chemotherapy after curative resection, the distant failure rate was 50%, with a median survival of 21.7 months. These findings are in agreement with a Japanese report on four patients with EPSCC [25], who underwent surgery followed by CRT and died with a median disease free survival of 18 months. Thus, overall, the response to various treatment modalities and the median survival time observed in the current study were discouraging.

Although chemotherapy with platinum-based regimens can be effective, the responses are short-lived. Since systemic recurrence frequently occurs outside the radiotherapy port after surgery, it is important to determine adequate adjuvant treatments and recommend more potent chemotherapy regimens.

In general, patients with ED at any site are treated initially with systemic combination chemotherapy regimens similar to those employed in PSCC. The combination of etoposide and cisplatin (EP) is one of the most frequently used of these regimens. In the 15 patients treated with platinum-based regimens, the response rate was 33%, and the median duration of survival was 2.5 months. Patients with ED who received supportive care had a median overall survival of 3 months (range, 1–5 months) and their tumors showed an aggressive natural history. In contrast, patients with ED who received chemotherapy had a median overall survival of 6 months (range, 1–25 months). The median survival times of patients with ED (6 months) and LD (23 months) reflect the aggressive nature of EPSCC and indicate the need for new therapeutic approaches in the treatment of this fatal disease.

In contrast to earlier studies, we found that SCC of the uterine cervix was not a prognostic factor (p = 0.28). However, SCC of the uterine cervix and GU system together showed a relatively favorable clinical course, with a median overall survival of 23 months. In contrast, SCC of the GI tract showed an aggressive clinical course, with a median overall survival of 10 months. However, it should be pointed out that 56% of patients with a GI primary tumor had ED at the time of diagnosis, whereas 100% patients with SCC of the uterine cervix had LD at the time of diagnosis and showed a favorable clinical course.

When a physician is confronted with EPSCC with mixed SCC and non-SCC histology, it is difficult to select a treatment regime that will act against both SCC and non-SCC. Even in patients showing a complete clinical response to chemotherapy, recurrent tumors will frequently consist of non-SCC clones. In the present patient group, however, we did not observe statistically significant differences in progression-free survival and overall survival rates between the 45 patients with pure SCC and the 16 patients with mixed SCC.

In summary, the response to various treatment modalities and the median survival time observed in

the present study were discouraging. Patients with GI primary tumors had poorer prognoses than those with primary tumors at other locations. Fifty six percent of patients with a GI primary tumor had ED at the time of diagnosis, whereas 100% of patients with SCC of the uterine cervix had LD at the time of diagnosis and showed a favorable clinical course. The majority of patients with LD SCC who underwent surgery, followed by adjuvant chemotherapy or chemoradiotherapy, showed tumor recurrence and/or systemic metastases. Clinical trials are needed to define adequate treatment strategies for EPSCC.

References

[1] Ricfhardson RL, Weiland LH. Undifferentiated small cell carcinomas in extrapulmonary sites. Semin Oncol 1982;9: 484–96.

[2] Ibrahim NBN, Briggs JC, Corbishley CM. Extrapulmonary oat cell carcinoma. Cancer 1984;54:1645–61.

[3] Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997;79:1729–36.

[4] Sengoz M, Abacioglu U, Salepci T, Eren F, Yumuk F, Turhal S. Extrapulmonary small cell carcinoma: Multimodality treatment results. Tumori 2003;89:274–7.

[5] Shamelian SO, Nortier JW. Extrapulmonary small cell carcinoma: Report of three cases and update of therapy and prognosis. Neth J Med 2000;56:51–5.

[6] Majhail NS, Elson P, Bukowski RM. Therapy and outcome of small cell carcinoma of the kidney: Report of two cases and a systemic review of the literature. Cancer 2003;97: 1436–41.

[7] Sykes AJ, Shanks JH, Davidson SE. Small cell carcinoma of the uterine cervix: A clinicopathological review. Int J Oncol 1999;14:381–6.

[8] Noguchi T, Takeno S, Kato T, Wada S, Noguchi T, Uchida Y, et al. Small cell carcinoma of the esophagus: Clinicopathological and immunohistochemical analysis of six cases. Dis Esophagus 2003;16:252–8.

[9] Chaudhary UB, Taksey JD, Johnson RD, Lewin DN. Small-cell cancers, and an unusual reaction to chemotherapy: Case 3. Small-cell carcinoma of the stomach. J Clin Oncol 2003; 21:2441–2.

[10] Lo Re G, Canzonieri V, Veronesi A, Dal Bo V, Barzan L, Zancanaro C, et al. Extrapulmonary small cell carcinoma: A single-institution experience and review of the literature. Ann Oncol 1994;5:909–13.

[11] Remick SC, Ruckdeschel JC. Extrapulmonary and pulmonary small-cell carcinoma: Tumor biology, therapy, and outcome. Med Pediatr Oncol 1992;20:89–99.

[12] Brenner B, Shah MA, Gonen M, Klimstra DS, Shia J, Kelsen DP. Small-cell carcinoma of the gastrointestinal tract: A retrospective study of 64 cases. Br J Cancer 2004;90: 1720–6.

[13] American Joint Committee on Cancer. AJCC Cancer Staging Manual. New York: Springer-Verlag; 2002.

[14] Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 1973;4:31–42.

[15] Van Der Gaast A, Verwey J, Prins E, Splinter TA. Chemotherapy as treatment of choice in extrapulmonary undifferentiated small cell carcinomas. Cancer 1990;65:422–4.

[16] Kaplan EL, Meier P. Known parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:475–81.

[17] Peto R, Peto J. Asymptotically efficient rank invariant procedures. J R Stat Soc 1972;135:185–207.

[18] Duguid JB, Kennedy AM. Oat-cell tumors of mediastinal glands. J Pathol Bacteriol 1930;33:93–9.

[19] Takaku H, Oka K, Naoi Y, Santoh N, Setsu Y, Mori N. Primary advanced gastric small cell carcinoma: A case report and review of the literature. Am J Gastroenterol 1999;94: 1402–4.

[20] Okuyama T, Korenaga D, Tamura S, Yao T, Maekawa S, Watanabe A, et al. The effectiveness of chemotherapy with cisplatin and 5-fluorouracil for recurrent small cell neuroendocrine carcinoma of the rectum: Report of a case. Surg Today 1999;29:165–9.

[21] Zanconati F, Falconieri G, Lamovec J, Zidar A. Small cell carcinoma of the liver: A hitherto unreported variant of hepatocellular carcinoma. Histopathology 1996;29:449–53.

[22] Kelsen DP, Weston E, Kurtz R, Cvitkovic E, Lieberman P, Golbey RB. Small-cell carcinoma of the esophagus: Treatment by chemotherapy alone. Cancer 1980;45:1558–61.

[23] Casas F, Ferrer F, Farrus B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: A review of the literature with emphasis on therapy and prognosis. Cancer 1997;80: 1366–72.

[24] Pignon JP, Arriagada R, Ihde D, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327:1618–24.

[25] Matsui K, Kitagawa M, Miwa A, Kuroda Y, Tsuji M. Small cell carcinoma of the stomach: A clinicopathologic study of 17 cases. Am J Gastroenterol 1991;86:1167–75.

[26] Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992;10: 890–5.