Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience

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Background: Esophageal small-cell carcinoma (SCC) is rare, highly malignant and the optimal treatment approach has not been defined.

Patients and methods: We report the largest single-institution retrospective review of patients with esophageal and gastroesophageal (GE) junction SCC.

Results: Twenty-five patients were identified, with complete records available for 22. Eighty-two percent were male, 82% had pure SCC histology and 86% of tumors were in the lower esophagus or GE junction. On the basis of the Veterans' Administration Lung Study Group criteria, 14 patients (64%) presented with limited disease (LD). Median survival was 19.8 months (range, 1.5 months to 11.2+ years); for LD patients, 22.3 months (range, 6 months to 11.2+ years); for extensive disease (ED) patients, 8.5 months (range, 1.5 months to 2.2 years, \( P = 0.02 \)). With a median follow-up of 38 months, six patients (27%) are alive, one with ED and five with LD. Two LD patients are alive and free of disease for >5 years. Four of the five LD patients who are long-term survivors received induction chemotherapy followed by chemoradiotherapy without surgery.

Conclusions: Our data indicate that patients with LD esophageal SCC treated with induction chemotherapy followed by consolidative chemoradiation can achieve long-term survival. The contribution of surgery remains unclear.

Key words: chemoradiotherapy, chemotherapy, esophagus, gastroesophageal junction, radiotherapy, small cell carcinoma, surgery

introduction

Small-cell carcinoma (SCC) of the esophagus is a rare and highly aggressive malignancy. Its incidence constitutes ~0.8%–2.4% of all esophageal malignancies [1]. Since it was first described in 1952, fewer than 300 cases have been described in the literature [2–4].

Because of the paucity of cases, the optimal therapy has not been defined. Given its histologic resemblance to pulmonary SCC [5, 6], SCC of the esophagus has commonly been treated with multimodality therapy, including chemotherapy or concurrent chemoradiotherapy, with or without surgery or surgery in conjunction with adjuvant chemotherapy [3, 7].

We report a retrospective analysis of the treatment and outcome of all cases of SCC of the esophagus and gastroesophageal (GE) junction at Memorial Sloan-Kettering Cancer Center (MSKCC).

patients and methods

The available medical records of all patients with a histologically proven diagnosis of SCC of the esophagus or GE junction seen at MSKCC from 1980 to 2005 were reviewed. The histological diagnosis of SCC was previously confirmed by the MSKCC Pathology department in all cases.

As there is no specific staging system for esophageal SCC, disease stage is presented according to two staging systems—the 2002 American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging system for esophageal cancer [8] and the Veterans' Administration Lung Study Group (VALSG) for primary pulmonary SCC [9]. This second system consists of two staging categories, limited disease (LD) and extensive disease (ED). LD is defined as tumor confined within a localized anatomic region with or without regional lymph node involvement. ED is defined as tumor outside locoregional boundaries [10]. As therapeutic decisions are normally based on the pulmonary SCC framework, therapy will be described based on VALSG staging.

Survival was analyzed as overall survival and calculated as the time from diagnosis to death. Survival was estimated using the Kaplan–Meier method [11]. Statistical analyses were carried out using the chi-square method.

results

patients characteristics

From 1980 to 2005, 25 patients with SCC of the esophagus or GE junction were identified. This constituted 1% (25 of 2393) of all patients with esophageal malignancies during that time period. Of these 25 patients, complete medical records were available for 22. Their general characteristics are listed in Table 1.
Tumor characteristics

Tumor characteristics are summarized in Table 2. By AJCC TNM staging, half (11 of 22) of the patients presented with stage I–III disease. Three patients (14%) had involvement of celiac lymph nodes with primary tumors in the lower esophagus (M1a or stage IVa disease). By VALSG criteria, 64% (14 of 22) of patients had LD (patients with stage IVa disease are classified as LD as the disease was confined to a single radiation field).

The choice of initial therapy depended on whether patients had LD or ED. Of the 14 patients with LD, three were treated with initial surgical resection. Of these three, one received no adjuvant therapy. Another patient received one cycle of adjuvant cisplatin/etoposide before declining further therapy because of poor tolerance. The third patient completed six cycles of adjuvant cisplatin/etoposide therapy.

The other 11 patients with LD underwent initial chemotherapy. Eight patients were treated with a platinum compound and etoposide (seven with cisplatin and one with carboplatin because of renal insufficiency), while one patient each received alternating cycles of cisplatin/etoposide with cisplatin/doxorubicin/vincristine (the CAV regimen), cisplatin/irinotecan, and paclitaxel (Taxol; Bristol Myers-Squibb, Princeton, NJ).

Of these 11 LD patients who received initial chemotherapy, four developed early progressive or metastatic disease. One patient was initially thought to have a poorly differentiated adenocarcinoma, with stage IVa disease with bulky celiac lymph nodes. He experienced locally progressive disease after receiving initial chemotherapy with paclitaxel. He then underwent a salvage esophagectomy, at which time pathology revealed a final diagnosis of SCC. He completed six cycles of adjuvant cisplatin/etoposide chemotherapy.

Fifty-two months later, he developed a bulky upper abdominal mass, biopsy proven to be consistent with recurrent SCC. He was treated with cisplatin/irinotecan chemotherapy but experienced progressive disease after one cycle.
Chemotherapy was then changed to cisplatin/etoposide, leading to a near complete response (CR) after four cycles. Concurrent radiotherapy was added to an additional two cycles of chemotherapy as consolidative treatment. He remains disease free 11.2 years after his initial diagnosis and 5.5 years after his recurrence. Representative computed tomography images at the time of recurrence are shown in Figure 1.

Another LD patient experienced local progression after initial chemotherapy with cisplatin/irinotecan and was changed to cisplatin/etoposide. She then experienced a near CR before the addition of concurrent radiation. The two other LD patients who experienced progression after induction chemotherapy developed distant metastases and received palliative chemotherapy.

One other LD patient who received initial chemotherapy was thought to have achieved a CR. He received prophylactic whole brain radiotherapy.

The remaining six patients who received initial chemotherapy were then treated with concurrent chemoradiotherapy. Five patients continued with platinum/etoposide during concurrent radiation, while one patient who had received cisplatin/etoposide as induction therapy was switched to cisplatin/5-fluorouracil. None of the patients who completed chemoradiotherapy subsequently underwent surgical resection.

Of the eight patients with ED, initial therapy consisted solely of chemotherapy. Patients received either sequential single-agent chemotherapy or combinations such as a platinum compound with etoposide (five patients), with irinotecan (two patients), with paclitaxel (one patient) or with vincristine (one patient), the CAV regimen (four patients) or the FOLFIRI regimen (one patient). Overall, cisplatin/carboplatin and etoposide were the most commonly administered regimens, with 18 of 22 patients (82%) receiving it at some point during their therapy.

clinical course

For all the 22 patients, median survival was 19.8 months (range, 1.5 months to 11.2+ years). All deaths were due to disease, with the exception of one patient who was lost to follow-up 3 months before her death, when she was thought to have no evidence of disease.

For the 14 patients with LD, median survival was 22.3 months (range, 6 months to 11.2+ years). For the eight patients with ED, median survival was 8.5 months (range, 1.5 months to 2.2+ years). The difference in survival between patients with LD and ED was statistically significant ($P = 0.02$) (see Figure 2).

At a median follow-up of 38 months, six patients remain alive, five without evidence of recurrent disease (all with initial LD) and one with disease (initially with ED). Two patients have been alive and free of disease for >5 years. Data for these six patients are presented in Table 3.

Of the 22 patients, 10 developed recurrent or progressive disease. Of these, 13 (72%) developed either locoregional recurrence or progression at known metastatic sites. Ten patients (56%) developed new metastases to a distant site. The most common site of distant metastases was the liver (4 of 10 patients or 40%). Significantly, brain metastases were uncommon and occurred only in one patient (5%).

Of the 14 patients with LD, 10 developed recurrent or progressive disease. All three patients who underwent initial surgical resection developed recurrence (one locoregional and two distant). The median survival for these patients was 21.9 months (range, 12.5–47.5 months).

Of the seven patients with LD who underwent planned induction chemotherapy and concurrent chemoradiotherapy without surgery, recurrence occurred in three patients (one locoregional and two distant). An eighth patient, who
underwent initial surgery and adjuvant chemotherapy, was salvaged at recurrence with chemoradiotherapy. The median survival for these patients has not been reached.

**discussion**

To our knowledge, this case series of 22 patients is the largest single-institution series for SCC of the esophagus and GE junction. Other modern series have reported 8–13 patients, with median survivals of 7–15.5 months [3, 7, 12]. A literature review of 199 patients reported in the literature described a median survival of only 8 months for patients with LD and 3 months for patients with ED [13]. Surgical resection was previously considered as the primary treatment of this disease. In an early report from our center, Kelsen et al. [6] first described a patient treated with chemotherapy alone. Subsequently, Nichols and Kelsen [14] reported the MSKCC experience from 1970 to 1987. The data indicated that esophageal SCC is a chemosensitive disease, although responses tend to be short lived. The current series includes five patients diagnosed and treated from 1980 to 1987.

Optimal therapy for this disease remains unclear, although several authors have advocated for surgery as part of therapy [3, 15]. In contrast, Casas et al. [13], in their literature review of 199 patients, identified chemotherapy (delivered with local therapy) as the factor associated with improved survival in LD patients.

Our data indicate that some patients treated based on a pulmonary SCC paradigm with induction chemotherapy followed by chemoradiotherapy, without surgery, can achieve long-term survival. The use of induction chemotherapy before definitive chemoradiotherapy also permitted early response assessment, with a needed change in chemotherapy identified in two patients progressing on induction treatment.

In comparison, none of the three patients who underwent initial surgical resection are alive; their median survival was not significantly different than the median survival for all LD patients. Therefore, surgery may not be necessary as part of initial therapy if a clinical CR is achieved to chemoradiotherapy. In carefully selected patients, it may be reserved for salvage after documented local failure following chemoradiotherapy.

The most common chemotherapy regimen that our patients received was a platinum compound and etoposide. It is interesting that two patients with LD progressed on therapy with cisplatin/irinotecan but were subsequently salvaged with cisplatin/etoposide. A randomized trial from Japan suggested superiority of cisplatin/irinotecan over cisplatin/etoposide for ED pulmonary SCC [16]. A separate report from Japan of 12 patients with LD and ED esophageal SCC presented in abstract form also indicated that cisplatin/irinotecan is an active regimen, with a response rate of 83% (including a CR in one patient) [17].

Finally, our data indicate that brain metastases are uncommon in esophageal SCC and were observed in only 1 of 22 patients. Unlike pulmonary SCC, where LD patients are routinely treated with prophylactic cranial irradiation because of the high incidence of central nervous system metastases [18], none of our long-term survivors received such therapy.

**references**