Esophageal Cancer Located at the Neck and Upper Thorax Treated with Concurrent Chemoradiation: A Single-Institution Experience

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Background: To characterize the treatment and outcome of patients with cervical and upper thoracic esophageal cancer, the authors retrospectively reviewed the 11-year experience from The University of Texas M. D. Anderson Cancer Center.

Methods: Thirty-five patients with M0 cervical or upper thoracic esophageal cancer and treated with concurrent chemoradiotherapy were analyzed. Median radiation dose was 50.4 Gy (range, 24.5–64.8) Gy delivered with 1.8-Gy daily fractions over 5.5 weeks. Chemotherapy was 5-fluorouracil based. Response after treatment was evaluated on the basis of radiography, biopsy, or both. The survival rates were calculated by means of the Kaplan-Meier method.

Results: The median follow-up for the surviving patients was 39 months. The actuarial 5-year overall survival (OS), cause-specific survival, disease-free survival, local relapse-free survival, and distant metastasis-free survival rates were 18.6%, 27.6%, 22.4%, 47.7%, and 57.0%, respectively. Patients who received a radiation dose of greater than or equal to 50 Gy had a higher complete response rate than those who received less than 50 Gy (79.2% versus 27.3%; $p = 0.003$). On multivariate analysis, radiation dose was the only protective factor associated with the rates of OS ($p = 0.006$), cause-specific survival ($p = 0.003$), and local relapse-free survival ($p = 0.001$); tumor stage was the only factor associated with rate of disease-free survival ($p = 0.007$).

Conclusion: Concurrent chemoradiotherapy is an effective treatment modality for patients with cervical and upper thoracic esophageal cancer. The authors' results suggest that a total radiation dose of 50 to 65 Gy with a concurrent chemotherapy regimen may improve local control and the OS rate in this rare type of esophageal cancer.

Key Words: Esophageal neoplasm, Cervical and upper thoracic, Concurrent chemoradiotherapy.

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Esophageal cancer located at the cervical and upper thoracic area is rare, representing less than 10% of esophageal cancer.[1] Some believe that the biological behavior of esophageal cancer at this location differs from those at the mid and lower esophagus or gastroesophageal junction, because they are mostly squamous-cell histology with local invasiveness and less prone to distant metastasis, and that they should be treated like head and neck cancer. In one study, a more favorable cause-specific survival was observed in patients with upper-third tumors than in those with middle- or lower-third tumors when treated with definitive chemoradiotherapy.[1]

Treatment is challenging because of the high risk of adjacent anatomical structure invasion, which precludes radical resection of the tumor. Even in patients with resectable tumor, surgery is often an unacceptable option because a total laryngectomy is usually required.[2] In four studies of patients with this type of cancer, those treated with surgery had morbidity rates of 60 to 70%, mortality rates of 7 to 11%, and a 5-year overall survival (OS) rate of 18 to 27%.[3–6]

Information on nonsurgical treatment of this tumor is sparse because of the rarity of its occurrence. In a few retrospective studies that focused on this subgroup of patients, concurrent chemoradiation was used as the treatment of choice.[7–12] Concurrent chemoradiotherapy has become a standard treatment for surgically unresectable esophageal cancer since the results of an intergroup, randomized, phase III trial (RTOG 8501) were reported in 1999, which included tumors of the thoracic esophagus.[13] There was no information on the location of the tumor or subgroup analysis on this group of patients. Because so little information is available on carcinoma at this location, we conducted a retrospective analysis of data from patients with cervical and upper thoracic esophageal cancer who had been treated with concurrent

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chemoradiotherapy, with or without induction chemotherapy, at our institution over a period of 11 years. To characterize the treatment and outcome for this group of patients, we analyzed the rates of clinical response, OS, cause-specific survival (CSS), disease-free survival (DFS), local relapse-free survival (LRFS), and distant metastasis-free survival (DMFS). We also investigated prognostic factors, particularly radiation dose, for the endpoints measured.

PATIENTS AND METHODS

Patient Population

From January of 1985 to December of 2001, a total of 703 patients with esophageal cancer were treated at the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center. Among them, 57 patients (8.1%) presented with a cervical or upper thoracic tumor. The medical records of these patients were retrospectively reviewed. To be included in our analysis, patients had to meet the following criteria: newly pathologically confirmed cervical and upper thoracic esophageal cancer (tumor located above the carina), no distant metastasis at presentation, and treatment with concurrent chemoradiotherapy but without surgery. We excluded patients if they had had distant metastases at presentation ($n = 10$), treatment by means other than surgery or radiotherapy ($n = 4$), treatment with surgery ($n = 3$), radiotherapy that had not been completed or followed up ($n = 2$), treatment with radiotherapy alone ($n = 1$), recurrent disease ($n = 1$), or two primary tumors both in the cervical and lower esophagus ($n = 1$). Thus, we included data on 35 patients in this analysis. We received approval for this retrospective review from our institutional review board, and we complied with all Health Insurance Portability and Accountability Act regulations.

Pretreatment Evaluations

The following pretreatment evaluations were performed on the 35 patients: all had a medical history interview, a physical examination, and laboratory studies, including complete blood count and biochemical survey; radiographic studies, including esophagograms ($n = 30$ [86%]), chest radiograph ($n = 34$ [97%]), computed tomographic (CT) scans of the chest ($n = 35$ [100%]), CT scans of the neck ($n = 13$ [37%]), and CT scans of the abdominal and pelvic scans ($n = 30$ [86%]); bone scan ($n = 6$ [17%]); and, when needed, CT or magnetic resonance imaging scans of the brain ($n = 3$ [9%]). Other specific studies included esophagogastroduodenoscopy with biopsy ($n = 35$ [100%]), endoscopic ultrasound of the esophagus ($n = 6$ [17%]), and bronchoscopic examination with or without brushing or biopsy ($n = 15$ [43%]).

Chemotherapy

Various induction chemotherapy regimens had been used: two to three cycles of 5-fluorouracil (5-FU) and cisplatin had been given to three patients; six cycles of 5-FU, cisplatin, and paclitaxel had been given to one patient; two cycles of 5-FU, carboplatin, and paclitaxel had been given to one patient; and two cycles of paclitaxel had been given to one patient. Concurrent chemotherapy had consisted of four different regimens of 5-FU alone or in combination with cisplatin, irinotecan, or carboplatin. Ten patients had received continuous infusions of 5-FU alone (250 mg/m^2) daily Monday through Friday for 5 weeks, and 10 patients had received continuous infusion of 5-FU (250 mg/m^2) daily Monday through Friday for 2 weeks (the number of weeks depended on the duration of radiotherapy). 5-FU plus cisplatin had been administered to 12 patients in one of the following three different regimens: six patients had received continuous infusion of 5-FU (750 mg/m^2) on days 1 through 5 and days 29 through 33, with cisplatin (75 mg/m^2) given on days 1 and 29; four patients had received continuous infusion of 5-FU (1000 mg/m^2) on days 1 through 4 and days 29 through 32 and cisplatin (75 mg/m^2) given on days 1 and 29; and two patients had received continuous infusion of 5-FU (750 mg/m^2) on days 1 through 5 and days 29 through 33 and cisplatin (15 mg/m^2) on days 1 to 5 and days 29 to 33. Three patients had been treated with regimens that did not include cisplatin. One of these had received continuous infusion of 5-FU (250 mg/m^2) daily Monday through Friday and carboplatin (area under the curve, 1.5) weekly for 5 weeks. The second of these three patients had received continuous infusion of 5-FU (300 mg/m^2) daily Monday through Friday and irinotecan (30 mg/m^2) weekly for 5 weeks. The third had received carboplatin alone (80 mg/m^2) every 3 weeks for 9 weeks.

Radiotherapy

Before January of 2000, conventional radiation techniques were used. For patients who were irradiated with less than or equal to 30 Gy, anteroposterior (AP) and posteroanterior (PA) fields were used. For patients who were irradiated with greater than 40 Gy, AP and PA fields were used to deliver a total dose of up to 40 Gy, and then oblique fields were used to spare the spinal cord. Beginning in January of 2000, a three-dimensional conformal radiotherapy technique was used. The initial target volume encompassed the primary tumor, with 5-cm cephalad and caudal margins and a 2-cm radial margin, with a field arrangement of AP + PA + oblique. The supraclavicular and midcervical nodal region was treated for all patients.

Typically, two fractionation schedules were used: the "rapid-fractionation" (30 Gy given in 10 fractions within 2 weeks) and standard (≥46 Gy given at 1.8–2.0 Gy per fraction daily, with five fractions administered weekly). The rapid fractionation was used based on the principle that the total radiation dose required to obtain a given biological effect decreases as the dose per fraction increases. A 30-Gy total dose of radiation given in 10 fractions was considered radiobiologically equivalent to a standard 5.5-week (50.4 Gy/28 fractions) program with a shortened overall treatment time. It was designed as a definitive treatment, combined with concurrent chemotherapy for esophageal, pancreatic, and periampullary carcinomas and used for prospective clinical trials during the early 1990s in this institution. Radiation therapy was primarily delivered with 18-MV photons, 6-MV photons, or both. The total radiation dose varied from 24.5 to 64.8 Gy, with a median dose of 50.4 Gy at 1.8 Gy per

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