Thirty-four Patients With Carcinoma of the Cervical Esophagus Treated With Chemoradiation Therapy

Bryan H. Burmeister, FRACR; Graeme Dickie, FRACR, FRACP; B. Mark Smithers, FRACS; Robert Hodge, FRACS; Karen Morton

Objective: To review the experience of 2 institutions in the management of localized carcinoma of the cervical esophagus with chemoradiation therapy.

Design: A series of 34 patients received chemoradiation therapy for a 5-year period. All patients were treated with curative intent. Three different regimens were used, all involving concomitant chemotherapy and high-dose radiation therapy. Data relating to toxic effects, local control of disease, and disease-free and overall survival were prospectively collected.

Setting: Two combined clinics at separate major hospitals where multidisciplinary care is the standard practice for this disease.

Patients: Patients with biopsy-proved carcinoma of the cervical esophagus.

Interventions: Patients received 3 different chemotherapy regimens. Two of the regimens used a combination of cisplatin and fluorouracil. The high-dose cisplatin regimen was a large dose of cisplatin (80 mg/m²) given on days 1 and 22 followed by a 96-hour infusion of fluorouracil (800 mg/m²) from days 2 to 5 and from days 23 to 26. The low-dose cisplatin regimen was cisplatin, 20 mg/m², from days 1 to 5 and from days 22 to 26 and the same 96-hour infusion of fluorouracil. The third regimen used fluorouracil alone. The mean radiation dose administered was 61.2 Gy in 29.6 fractions during 41.8 days using 4- or 6-mV photons and a shrinking field technique.

Results: The results of treatment have shown a high rate of local control, although some patients developed metastases. The local complete response rate following treatment was 91%, and the rate of local control of disease was 88%. The projected actuarial 5-year survival rate was 55%. Death from other causes was common. The acute toxic effects of the treatment were acceptable, with only 5 patients requiring nasogastric feeding or gavage. Two patients died of complications related to strictures.

Conclusion: Concomitant chemoradiation therapy should be the treatment of choice for carcinoma of the cervical esophagus.


Until recently the treatment of carcinoma of the cervical esophagus has been dominated by surgical resection. Surgery requires the removal of the esophagus, hypopharynx, and larynx, thus leaving the patient with a permanent tracheostomy. Some centers have managed these tumors with radical radiation therapy, although the reported survival rates have been less than those in patients treated with surgical resection. Tumors located within the upper or middle part of the thoracic esophagus have usually been treated with radiation therapy if they are not suitable for surgical resection. Limited information is available on the results of treatment of cervical esophageal cancers, because they have often been included with carcinomas of the hypopharynx, especially when it comes to surgical management. Recently, the results of radiation therapy, in terms of both local control and survival, for esophageal cancer have improved with the addition of concomitant chemotherapy, principally with the use of cisplatin and fluorouracil. A recent large multicenter study conducted in Australia and New Zealand showed a trend toward improved survival of patients with tumors in the upper third of the thoracic esophagus. This article is a retrospective review of 34 patients with esophageal cancer who were treated with concomitant chemoradiation with the hope that the response to therapy would result in effective local control of the disease with conservation of the larynx.
PATIENTS AND METHODS

From January 15, 1991, to January 31, 1996, 34 patients with carcinoma of the cervical esophagus were enrolled in the study. Patients were included if the tumor appeared to arise within the cervical esophagus between the criocopharyngeal muscle and the thoracic inlet. However, some patients had tumors extending into the postcricoid region and the upper thoracic esophagus. The ratio of men to women was 3.3:1. The mean age of the patients was 63.1 years, with a range of 38 to 79 years. Of the 34 patients, 32 had squamous cell carcinomas, of which 4 were well differentiated, 21 moderately differentiated, and 7 poorly differentiated. The remaining 2 patients had adenocarcinomas (one described as adenoid cystic carcinoma) presumably arising in minor salivary glands in the cervical esophagus or a gastric mucosal inlet patch. The clinical staging of the 34 patients according to the International Union Against Cancer stage grouping was as follows: 4 were in stage I with T1 N0 M0 classification, 20 were in stage II with T2 N0 M0 or T3 N0 M0 classification, 7 were in stage III with T1 N1 M0 or T2 N1 M0 classification, and 3 were in stage IV with T3 N1 M0 or T4 NX M0 classification. The patients presented at 1 of 2 separate multidisciplinary clinics for a decision regarding management. Each patient was evaluated by a surgeon and a radiation oncologist. A panendoscopy and biopsy of the tumor were performed in all cases. Surgical removal of the tumor would have required a laryngectomy to obtain adequate clearance. Consequently, all patients were offered a course of radical radiation therapy combined with concomitant chemotherapy as definitive treatment. Surgery was reserved for local recurrence. An immobilization shell was constructed prior to simulation and radiation planning. Radiation planning was performed with the aid of computed tomography to optimize the radiation doses (obtaining the highest dose) to the tumor, avoiding damage to the spinal cord. Radiation was administered using a linear accelerator producing 4-MV or 6-MV photons. The treatment frequency was given in 2 or 3 phases using shrinking fields. The aim was to deliver at least 50 Gy to a large area, including the draining lymph nodes, followed by a boost to the tumor and a 2- to 3-cm margin around the tumor. The mean radiation dose administered was 61.2 Gy in 29.6 fractions during 41.8 days. The lowest radiation dose was 50.4 Gy in 20 fractions during 32 days, and the highest dose was 65 Gy in 33 fractions during 45 days.

Three chemotherapy regimens were used. Younger and more physically fit patients with adequate renal function were given cisplatin and fluorouracil, whereas elderly patients with esophagitis renal function were given fluorouracil alone. Of the regimens containing both cisplatin and fluorouracil, there were 2 variations. One regimen consisted of a large bolus of 80-mg/m² cisplatin (high-dose) given on day 1 followed by a 96-hour infusion of fluorouracil (800 mg/m² daily). The second regimen consisted of 20-mg/m² cisplatin (low-dose) for days 1 to 5 together with the same 96-hour infusion of fluorouracil. The regimens were repeated after 3 weeks or when the patient’s blood cell count had returned to normal. Eight patients received only 1 course of chemotherapy. The chemotherapy schedules for the 34 patients were as follows: 24 received 80-mg/m² cisplatin for days 1 and 22 and 800-mg/m² fluorouracil for days 2 to 5 and 23 to 26; 8 received 20-mg/m² cisplatin for days 1 to 3 and 22 to 26 and 800-mg/m² fluorouracil for days 2 to 5 and 23 to 26; and 2 received 800-mg/m² fluorouracil for days 2 to 5 and 23 to 26. During therapy, patients were monitored for signs of toxic effects. Maintenance of nutrition with the involvement of dietitians was emphasized when possible. In patients who were unable to swallow as a result of tumor obstruction or esophagitis due to severe radiation, percutaneous gavage was instituted. Treatment was suspended or discontinued when excessive toxic levels were observed. Following treatment, an initial follow-up endoscopy was performed 6 weeks after therapy and thereafter at monthly intervals depending on whether the patient experienced dysphagia. Patients were assessed with regard to their response to therapy on the basis of the clinical impression of the endoscopist, and biopsies of the region were only performed if there was a possibility of tumor recurrence. At follow-up, radiological investigations were only performed if they were clinically indicated. Also, regular clinical examinations were performed at 3-month intervals. Overall actuarial survival rates and progression-free survival rates were calculated using the Kaplan-Meier method. Comparison of the survival rates, according to the chemotherapy regimen given in each tumor stage group, was performed using the log-rank test.

RESULTS

At the time of analysis, the median follow-up period was 55 months, with a range of 34 to 82 months. The local response rate to therapy following treatment was excellent. Of the 34 patients, endoscopic observation showed 31 (91.1%) had a complete response, 2 (5.9%) had a partial response, and 1 (2.9%) had progressive disease. Six patients developed distant metastases involving the lung (1), liver (1), axillary lymph nodes (1), bone (2), and distal esophagus (1). At the time of analysis, 15 patients were healthy and free of disease, and 1 patient was alive with a local recurrence, which was detected endoscopically 14 months after commencing treatment. Of the 18 remaining patients, 9 died of their disease (3 from persistent local disease and 6 from metastases), and 2 patients died as a result of treatment: one died of a severe hemorrhage following attempted surgical correction of a severe stricture and the other patient developed a tracheoesophageal fistula and died of pneumonia following repeated dilation of a moderate stricture. The remaining 7 patients died of other causes, which were carcinoma of the tongue (2), lung cancer (1), pancreatitis (1), acute gastric hemorrhage (1), stroke (1), and cardiac failure (1). Of the 3 patients who had persistent disease in the absence of distant metastases, surgical salvage of the esophagus was not attempted in view of the risks associated with the previous radiation therapy and the poor nutritional status of these patients; all these patients died of their disease within a few months. The patient who had a recurrence following a complete response remained asymptomatic and refused salvage surgery. The overall actuarial survival rate for the study group was projected to be 55% at 5 years. The survival curve is shown.
in Figure 1. Patients with clinical stage III tumors appeared to have a poorer disease-free survival than patients with stage I and stage II tumors, although insufficient numbers of patients with stage III tumors did not make this difference significant (P = .80). We also analyzed survival according to whether the patient received high-dose or low-dose cisplatin with radiation therapy. There was no significant difference between the 2 regimens in terms of overall and disease-free survival (P = .86 and P = .87 for Figure 2 and Figure 3, respectively).

Toxic effects of the treatment were assessed and graded according to the toxicity criteria of Miller et al.7 Grade 4 esophagitis (necessitating nasogastric feeding or gavage) occurred in 5 patients. All other patients had moderate esophagitis that was relieved by local analgesics. Myelosuppression (grade 3+) following chemotherapy was observed in 4 patients, necessitating delay or discontinuation of further chemotherapy. A moderate-to-severe skin reaction occurred in most patients on the neck. Two patients had pneumonia due to aspiration, and 1 patient developed temporary cardiac failure following an initial infusion of fluorouracil. In the longer term, strictures appeared to be the most notable late effect of therapy: 19 patients had no strictures, 11 patients developed mild strictures that did not require dilation, 4 patients developed strictures requiring repeated dilation, and 1 patient developed a severe stricture that did not respond to dilation. In the patient with a severe stricture, the attempted corrective surgery failed and resulted in death. Laryngeal dysfunction was commonly reported as an acute event associated with edema related to the radiation therapy. Unfortunately, long-term effects on speech function were not evaluated, but virtually all patients maintained acceptable speech capacity. One patient developed neurological toxic effects, exhibiting Lhermitte sign (transient shocklike symptoms on head flexion) 7 months after completing therapy.

**COMMENT**

Carcinoma of the cervical esophagus has traditionally been managed with the use of radical surgery.6,9 Surgery involves removal of the esophagus, hypopharynx, and larynx, leaving the patient with a permanent tracheostomy. Radiation therapy has been used in some centers but has led to inferior results compared with surgical resection. Results from the Memorial Sloan-Kettering Cancer Center, New York, NY, showed that the mean survival was 17 months for all patients who underwent surgical resection, including those treated palliatively.10 Experience at other centers, such as the University of Verona, Verona, Italy, has also shown disappointing results with the use of radical surgery; they reported a mortality rate of 8.8%. In our study, we believe the initial treatment with concomitant chemotherapy and radiation therapy offered patients a chance of retaining their larynxes and acceptable treatment-related morbidity and mortality. Radiation therapy as a sole modality for the treatment of carcinoma of the cervical esophagus has been used in some institutions. Kalavathi11 conducted one of the largest series involving postcricoid tumors, in which the 5-year survival rate of 103 patients treated for cure with radiation alone was 19.1%. In another major study,12,13 conducted...
in Gainesville, Fla, the overall 5-year survival rate of 34 patients was 24%. For esophageal cancer, there is now little doubt that the addition of chemotherapy to a schedule of radical radiation therapy improves both local response and survival. Soto Parra presented a review of patients with cervical esophageal carcinoma treated definitively with chemoradiation therapy at the Program and Proceedings of the the American Society of Clinical Oncology, May 17-20, 1997. In that series, there were 37 patients treated for 8 years with chemotherapy using cisplatin and fluorouracil and radiation doses of 50 to 60 Gy. The complete response rate in that series was only 24 (65%), and the 3-year survival rate was 38%. However, 20 (54%) of the patients in that study had stage III disease compared with only 3 (8.3%) in our series. This addition of chemotherapy to a schedule of radical radiation is clearly the major reason for the excellent response and local control in our patients. Our 5-year survival rate of 55% compares favorably with the 4-year survival rate of 62% reported by Denham et al for tumors of the upper-third thoracic esophagus treated with definitive chemoradiation therapy. These figures also show considerable improvement compared with the 5-year survival rate quoted by Kelley et al, although 25% of those in this series were palliatively treated patients. In our series, there was no difference in the local response rates between the different chemotherapy regimens. The omission of cisplatin in 2 patients due to comorbidity also did not seem to compromise local response, in that local control was achieved in both patients. Achieving local control without cisplatin has been supported by other data from our center for patients with esophageal cancer treated with radiation and concomitant fluorouracil alone. However, the main concern is the possible increased toxic effects, especially stricture formation, due to radiation. In the study conducted by Soto Parra et al, 3 patients had notable acute complications, including 1 death from the toxic effects of the treatment. The rate of stricture was not noted. We believe that the short-term morbidity associated with chemoradiation therapy is acceptable given the availability of gavage that can be instituted when necessary. Although the mean follow-up in our series was short, the early results are encouraging. Although 2 patients had late treatment-related deaths, the mortality is probably equivalent to that in aggressive surgery. The complete response rate of 92% (with only local tumor relapse in 1 patient) represents an acceptable local outcome. In this group of tumors of the upper aerodiges-

tive tract, there is a definitive incidence of second primary malignancies and other fatal conditions associated with smoking and alcohol consumption that may cause premature deaths in these patients. Given our results, we encourage clinicians to treat the condition of carcinoma of the cervical esophagus with concomitant chemoradiation therapy.

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Corresponding author: Bryan H. Burmeister, FRACR, Queensland Radium Institute, 31 Raymond Terr, South Brisbane, Australia 4101.

REFERENCES