The Effects of Neoadjuvant Chemoradiation on pTNM Staging and Its Prognostic Significance in Esophageal Cancer

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For esophageal cancer, it is not clear if pathologic TNM staging after chemoradiation and resection will have the same prognostic significance compared with patients who undergo resection only. From 1995 to 2004, prospectively collected data from 279 patients with intrathoracic squamous cell cancers were analyzed. Patients were given chemoradiation either as part of a randomized trial comparing neoadjuvant chemoradiation with surgical resection alone, or because of advanced disease at presentation. One hundred seventy patients had surgical resection only (surgery), and 109 had neoadjuvant chemoradiation (CRT plus surgery). In the surgery group, pT1, 2, 3, and 4 disease was found in 15, 17, 104, and 34 patients, respectively; their respective pN1 rates were 13.3%, 29.4%, 57.7%, and 64.7%, $P < 0.01$. In CRT plus surgery, pT0, T1, 2, 3, and 4 were found in 48, 12, 23, 21, and 5 patients, respectively; their respective pN1 rates were 31.3%, 16.7%, 21.7%, 52.4%, and 20%, $P = 0.44$. Logistic regression analysis of factors predictive of pN1 showed that pT stage correlated with pN1 status ($P = 0.005$) in the surgery group, but not for the CRT plus surgery group. Cox regression analysis demonstrated that in the surgery group, pT, pN, and R category, and overall pTNM stage, were independent prognostic factors, whereas pN, R category, and gender were identified as relevant for CRT plus surgery. After chemoradiation, pT and overall pTNM stage groupings were not as clearly prognostic as in patients without prior therapy. Nodal status remains an important prognostic factor. (J GASTROINTEST SURG 2006;10:1301–1311)

KEY WORDS: Esophageal neoplasm, chemoradiation, multimodality treatment, staging, prognosis

Immediate surgical results of esophagectomy for cancer have improved. In dedicated centers, a mortality rate of below 5% can be achieved.[1–4] Prolonging long-term survival is a goal more difficult to attain. Prognosis for esophageal cancer remains poor throughout the world. In selected centers and in subgroups of patients who undergo radical esophagectomy, 5-year survival rates of 40% or above could be achieved.[5–7] Selection bias is difficult to disprove, and such encouraging results are infrequently seen. In most reports, a 20% 5-year survival rate is recorded.[8,9]

In recent years, neoadjuvant therapy involving chemotherapy and/or radiotherapy is commonly used as an adjunct to surgical resection.[10,11] Despite the equivocal data from randomized controlled trials that these treatments can result in better prognosis compared with surgery alone, they are frequently applied with an aim to downstage tumor—increasing the resection rate (especially R0 resection)—and to improve survival.[12–17] After neoadjuvant therapy, however, clinical restaging is difficult with conventional techniques such as CT scan or endoscopic ultrasound. Positron emission tomography scan shows some promise, but how it should be integrated into clinical practice, and whether it can be used to predict long-term survival or not requires further evaluation.[18]

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Among other factors investigated, pathological TNM stage after resection has been the gold standard in prognosis stratification, and the relationship between advancing pTNM stage and poor survival is well established. It has been our observation however, that after chemoradiation, the primary tumor is often sterilized, but persistence of nodal disease exists. It is therefore hypothesized that neoadjuvant therapy may alter the relationship between the different components of the pTNM system, such as the intercorrelation of pT and pN status, and that the postchemoradiation pTNM stages may have different prognostic implications compared with patients without prior therapy. These factors are investigated in a large group of patients undergoing surgical resection, with or without neoadjuvant chemoradiation.

METHODS

From 1995–2004, 471 patients with intrathoracic squamous cell carcinomas without prior treatments were managed at the Department of Surgery, The University of Hong Kong at Queen Mary Hospital. Patients who had cancers located in the cervical esophagus, tumors that involved the gastroesophageal junction, and cancers of other cell types were excluded from this study. Patients with synchronous or history of nonesophageal malignancies were also excluded, so that the influence of other unrelated tumors on survival was prevented. Surgical resection was carried out in 279 patients (59.2%), of whom 170 had surgical resection only and 109 received preoperative chemoradiation therapy. Data were captured in a prospectively collected database. These patients were the subjects of the present study.

The management rationale and protocols at the authors' institution have been described previously.[19] Patients were managed in an individualized manner determined by both patient (performance status, comorbidities) and tumor (stage, location) characteristics. Surgical treatment was the preferred treatment option. Patients were selected for nonsurgical treatment if they had locally advanced unresectable disease, or nonlocal-regional metastases, when medical-surgical risks were prohibitive, or in those who declined surgery.

For tumor imaging and staging purposes, all patients had a barium contrast study, an endoscopy, bronchoscopy, and since May 1996, endoscopic ultrasound examination. An ultrasound of the neck and CT scan of the thorax and abdomen were carried out. Positron emission tomography scans were available for most patients since July 2002.

The surgical techniques are described in brief: for most tumors in the middle and lower third of the esophagus, a Lewis-Tanner esophagectomy via an abdominal-right thoracotomy approach was preferred. For patients who had a tumor of the superior mediastinal segment, a three-phase esophagectomy was carried out. In this operation, usually a right-sided thoracotomy was performed first for esophageal mobilization; a synchronous laparotomy and left cervical incision then provided access for gastric and cervical esophageal mobilization, followed by a gastric pull-up to the neck, either by the posterior mediastinal or by the retrosternal route for cervical esophagogastrostomy. In patients who had limited cardiopulmonary reserve for whom a thoracotomy was judged to be of high risk, a transhiatal esophagectomy was performed. This method was mainly used for tumors of the lower esophagus. This method was uncommonly performed in the study period because the preferred approach was transthoracic and thoracoscopic esophagectomy has also largely replaced the need for transhiatal esophagectomy.[20] Altogether, 16 patients underwent thoracoscopic esophagectomy.

Lymphadenectomy usually involved a two-field lymphadenectomy with dissection of lymph nodes around the celiac trifurcation, and also an infracarinal mediastinal lymph node dissection. Lymph nodes of the superior mediastinum were sampled, but complete clearance of nodal tissues around the paratracheal area along the recurrent laryngeal nerves was not usually performed unless suspicious lymph nodes were encountered. Similarly, cervical lymphadenectomy was not carried out routinely unless there was evidence of disease because our study of recurrence patterns suggested limited value of neck dissection,[21] and that survival advantage of cervical lymphadenectomy was not proven.[22,23] In patients with obviously palliative resection, a more limited lymphadenectomy was carried out.

Reconstruction of intestinal continuity was usually restored with a gastric conduit placed in the right thoracic cavity (after Lewis-Tanner esophagectomy) or via the orthotopic route when the anastomosis was carried out in the neck. In the obviously palliative cases where residual mediastinal disease was evident, the retrosternal route was chosen. The colon was used in patients with a prior gastrectomy, the right ileocolon being the preferred conduit.[24] All these surgical techniques have been described.[25,26]

Processing of the resected surgical specimens started in the operating room. The operating surgeons dissected the different nodal stations separately and labeled them for further histological examination. Individual nodes were not dissected,