GENERAL THORACIC SURGERY

STAGE II ESOPHAGEAL CARCINOMA: THE SIGNIFICANCE OF T AND N

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Objective: Stage II esophageal carcinomas are a heterogeneous group of uncommon malignant tumors that include both node-negative (IIA; T2 N0 M0 and T3 N0 M0) and node-positive (IIB; T1 N1 M0 and T2 N1 M0) carcinomas. The purpose of this study was to evaluate this heterogeneity and to identify predictors of improved survival. **Results:** Ninety-four of 345 patients undergoing esophageal resection at the Cleveland Clinic Foundation between 1985 and 1994 had stage II carcinomas; 70 stage IIA (24 T2 N0 M0 and 46 T3 N0 M0) and 24 stage IIB (9 T1 N1 M0 and 15 T2 N1 M0). Pathologic stage and T and N status were the only identifiable predictors of survival. Stage IIA survival was significantly better than stage IIB ($p = 0.01$). T2 N0 M0 survival was not different from T1 N0 M0 survival ($p = 0.83$). T3 N0 M0 survival was significantly worse than T1 N0 M0 ($p = 0.03$) and intermediate between T2 N0 M0 survival ($p = 0.06$) and T1 N1 M0 and T2 N1 M0 survivals ($p = 0.07$). T1 N1 M0 and T2 N1 M0 survival was not significantly different from T3 N1 M0 survival ($p = 0.63$). **Conclusions:** (1) N1 disease is the principal predictor of reduced survival and N1 is independent of T. Therefore the distinction between T1 N1 M0, T2 N1 M0, and T3 N1 M0 carcinomas is not warranted. (2) N0 disease is the principal predictor of improved survival but N0 is not independent of T. T1 N0 M0 and T2 N0 M0 survivals are similar and therefore distinction between these subgroups is not warranted. T3 N0 M0 survival is intermediate between T1 N0 M0 and T2 N0 M0 carcinomas and between T1 N1 M0, T2 N1 M0, and T3 N1 M0 carcinomas. Therefore stratification by T for N0 carcinomas is warranted. (J Thorac Cardiovasc Surg 1996;111:935-40)

Until 1987 staging of esophageal carcinomas was a neglected practice. Most physicians found little use for the unwieldy staging systems, because the majority of patients had advanced disease, treatment had little impact on survival, and no clear correlation existed between stage and survival. Coincident with the introduction of a new staging

system,^{1,2} there came significant advances in clinical staging technology^{3,4} and the recognition of remarkable changes in the epidemiology of esophageal carcinoma, characterized by a dramatic increase in the relative prevalence of adenocarcinoma.⁵

Today the stage of an esophageal carcinoma, as defined by its anatomic extent, is the best single prognosticator available. The present staging system is TNM based (Table I).⁶ The status of the primary tumor (T) is defined by depth of invasion, and the status of regional lymph nodes (N) is characterized by the absence (N0) or presence (N1) of metastases. Distant metastases are either absent (M0) or present (M1). These TNM descriptors are grouped into stages with a presumed similar behavior and prognosis (Table I).

Unfortunately, the majority of patients with esophageal carcinomas still have stage III or IV disease when first examined. Recently, the growing appreciation of the malignant potential of Barrett's

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Read at the Twenty-first Annual Meeting of The Western Thoracic Surgical Association, Coeur d'Alene, Idaho, June 21-24, 1995.

Received for publication June 21, 1995; revisions requested Oct. 2, 1995; revisions received Oct. 20, 1995; accepted for publication Dec. 21, 1995.

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0022-5223/96 \$5.00 + 0 12/6/71451

Table I. *The staging of esophageal carcinomas*

T: Primary tumor				
Tis	High-grade dysplasia			
T1	Tumor invades the lamina propria, muscularis mucosa, or submucosa			
T2	Tumor invades the muscularis propria			
T3	Tumor invades the periesophageal tissue			
T4	Tumor invades adjacent structures			
N: Regional lymph nodes				
N0	No regional lymph node metastases			
N1	Regional lymph node metastases			
M: Distant metastasis				
M0	No distant metastasis			
M1	Distant metastasis			
<i>Stage grouping</i>				
Stage 0		Tis	N0	M0
Stage I		T1	N0	M0
Stage Ila		T2	N0	M0
		T3	N0	M0
Stage Iib		T1	N1	M0
		T2	N1	M0
Stage III		T3	N1	M0
		T4	Any N	M0
Stage IV		Any T	Any N	M1

esophagus and the increasing use of surveillance endoscopy have resulted in more frequent diagnoses and resections of stage I esophageal carcinomas.⁷ Although the natural histories of stage I and stage III carcinomas have been studied, the behavior of stage II carcinomas is less well characterized.

Stage II esophageal carcinomas are a heterogeneous group of uncommon malignant tumors that include both node-negative (stage IIA; T2 N0 M0 and T3 N0 M0) and node-positive (stage IIB; T1 N1 M0 and T2 N1 M0) carcinomas. In this study we examined the natural history of surgically treated and pathologically staged stage II esophageal carcinomas to identify predictors of improved survival and to determine if the subgroups comprising this stage have similar behaviors and prognoses.

Patients and methods

Patient selection. The hospital records of all patients who underwent surgical resection of an esophageal carcinoma at the Cleveland Clinic Foundation between September 1985 and October 1994 were retrospectively reviewed. Pathologic TNM stage, age, gender, histologic cell type, and the use of adjuvant therapy were recorded for patients with pathologic stage I, II, and III (T3 N1 M0)

carcinomas. Patients with no residual carcinoma after induction therapy and resection, stage 0, advanced stage III (T4), and stage IV carcinomas were recorded but not analyzed.

Surgical therapy. Esophageal resection, lymphadenectomy, and reconstruction with the stomach were performed by three different surgical approaches. Our approach to surgical resection is based on clinical staging and the location of the primary carcinoma. Patients preoperatively believed to have high-grade dysplasia or clinical stage I carcinomas (T1 N0 M0) of the lower thoracic esophagus, as well as patients with advanced carcinomas of the lower thoracic esophagus who were not candidates for thoracotomy, underwent a transhiatal esophagectomy with lymph node sampling. Rarely, these resections were completed via a laparotomy alone. Patients who were candidates for thoracotomy and were believed clinically to have carcinomas more advanced than stage I or those patients with midthoracic or upper thoracic esophageal carcinomas underwent esophageal resection via a left thoracoabdominal approach, or alternatively a right thoracotomy and upper abdominal midline laparotomy. A complete lymphadenectomy was performed in these patients. Patients with cervical esophageal carcinomas involving the larynx and pharynx underwent a pharyngolaryngoesophagectomy via a transhiatal approach. Esophagogastric anastomoses were constructed in either the neck or chest by either a sutured or stapled technique.

Adjuvant therapy. During this period two induction therapy protocols of chemotherapy and chemoradiation therapy were offered to selected patients with clinically advanced carcinomas.⁸⁻¹⁰ Postoperative adjuvant radiation therapy was offered to selected patients with pathologically advanced carcinomas. These treatments were recorded for all patients.

Pathologic analysis. The following standardized surgical pathology protocol for esophageal resection specimens is used at the Cleveland Clinic Foundation. The resection margins, the esophageal body, the gastroesophageal junction, and the regional lymph nodes were extensively sampled. When gross lesions were identified, multiple sections of each lesion including the area of deepest penetration of the esophageal wall were evaluated. When a gross lesion was not identified, at least ten sections of the esophageal body and gastroesophageal junction were evaluated. All separately resected lymph nodes and all lymph nodes that were grossly identified in the resection specimen were evaluated pathologically. When small enough, the entire lymph node was submitted, and two levels of that node were examined histologically. Larger lymph nodes were bisected and two levels of each of the two portions of the bisected lymph node were examined.

Patient follow-up. The minimum follow-up consisted of an annual physical examination, chest roentgenogram, complete blood count, and serum chemistries. When indicated, computed tomographic scanning, esophagogastroduodenoscopy, and endoscopic esophageal ultrasonography were performed. All deaths and causes of death were recorded. Sites of recurrence were noted. All living patients were contacted before data analysis and follow-up was obtained for all patients.

Table II. Patient demographics

	I	IIA	IIB	III (T3 N1 M0)
Age (yr)				
Mean (SD)	64 (12)	64 (11)	60 (10.2)	63 (10.6)
Range	35-78	31-84	36-83	26-84
Gender (No.)				
Male	32	52	22	113
Female	2	18	2	19
Histology (No.)				
Adenocarcinoma	30	41	18	114
Squamous cell	4	24	5	15
Large cell	0	1	0	0
Adenosquamous	0	4	1	3

Statistical analysis. Categorical factors were summarized by use of frequencies and percentages and continuous measures by use of the mean, standard deviation, median, and range. Survival time was calculated from the date of the operation to the time of death or most recent follow-up. The Kaplan-Meier method was used to estimate survival and the log rank test was used to test for differences in survival distributions between subgroups of interest. All tests were performed using a 5% significance level, with no formal adjustment for multiple testing.

Results

A total of 345 patients underwent esophageal resection during the 11-year period. Eighty-four patients had no residual carcinoma after induction therapy and resection, stage 0, advanced stage III (T4), or stage IV carcinomas and are not further discussed. One patient had resection of a T0 N1 M0 carcinoma after adjuvant therapy and has been excluded from analysis, because no staging group exists for this patient. Thirty-four patients had resection of stage I esophageal carcinomas and 132 patients had resection of stage III (T3 N1 M0) esophageal carcinomas. Ninety-four (27.2%) patients had resection of stage II carcinomas. There were 70 (20.2%) stage IIA carcinomas: 24 T2 N0 M0 and 46 T3 N0 M0. There were 24 (7.0%) stage IIB carcinomas: 9 T1 N1 M0 and 15 T2 N1 M0. Patient characteristics are summarized in Table II.

Seven (7.4%) patients with stage II disease underwent transhiatal esophagectomy. A thoracic incision was used in 84 (89.4%) patients; 35 had an Ivor Lewis approach and 49 had a thoracoabdominal approach. Three patients (3.2%) underwent laparotomy for esophagogastric resection. Fifty-six (59.6%) patients had no adjuvant therapy, and 38 (40.4%) patients had perioperative adjuvant therapy

Table III. Adjuvant therapy

	Induction	Postoperative
Chemotherapy	7	0
Chemoradiation	13	8
Radiation	0	10
Total	20	18

(Table III). Among the patients who received adjuvant therapy, there were 25 stage IIA (10 T2 N0 M0 and 15 T3 N0 M0) and 13 stage IIB (six T1 N1 M0 and seven T2 N1 M0) carcinomas.

Thirty-four (36%) patients were alive at most recent follow-up, 28 with stage IIA and six with stage IIB disease. One patient with stage IIB disease was alive with a distant recurrence in the liver. There were 60 (64%) deaths; 42 of these patients had stage IIA disease and 18 stage IIB disease. There were two (2.2%) deaths within 30 days of operation; both patients who died had stage IIA disease. Two additional patients died of late complications during the initial hospitalization. These four patients account for the 4.4% in-hospital mortality (three with stage IIA and one with stage IIB disease). Seven (7.5%) patients died without evidence of recurrent carcinoma, six with stage IIA and one with stage IIB disease. Forty-nine (52.1%) patients died of recurrent carcinoma, 33 with stage IIA and 16 with stage IIB carcinoma. Locally recurrent carcinoma was documented in 23 patients, 15 with stage IIA and eight with stage IIB disease. Distant metastases were documented in 27 patients (26 have died); 18 had stage IIA and nine had stage IIB disease.

Survival differed by stage (Table IV). Survival for patients with stage IIA disease was significantly better than for those with stage IIB disease ($p = 0.01$) (Fig. 1). Survival for patients with stage I disease was better than for those with stage IIA disease, but the difference was not statistically significant ($p = 0.09$). Survival for stage IIB was not significantly different from that for stage III (T3 N1 M0) ($p = 0.63$).

Survival differed by T and N status (Table IV, Fig. 2). Survival of patients with T2 N0 M0 disease did not differ from that of patients with T1 N0 M0 disease ($p = 0.83$). Survival of patients with T2 N0 M0 disease was better than but not statistically different from the survival of patients with T3 N0 M0 disease ($p = 0.06$). Survival of patients with T3 N0 M0 disease was statistically significantly worse than that of patients with T1 N0 M0 disease ($p = 0.03$).

Fig. 1. Stage IIA and stage IIB survival.

Fig. 2. Stage II TNM subgroup survival.

Table IV. Survival information by stage and TNM subgroups

Stage	N	Five-year survival (%)	Median survival time (mo)
I: T1 N0 M0	34	50	56
IIA	70	33	27
T2 N0 M0	24	50	28
T3 N0 M0	46	26	26
IIB	24	—	20
T1 N1 M0	9	—	23
T2 N1 M0	15	—	20
III: T3 N1 M0	132	10	13

Log rank test *p* values:

T1 N0 M0 versus T2 N0 M0 = 0.83.

T1 N0 M0 versus T3 N0 M0 = 0.03.

T2 N0 M0 versus T3 N0 M0 = 0.06.

T3 N0 M0 versus IIB = 0.07.

IIB versus T3 N1 M0 = 0.63.

Survival of patients with T1 N1 M0 and T2 N1 M0 disease did not differ from that of patients with T3 N1 M0 disease ($p = 0.63$). Survival for these patients with stage IIB disease was worse than, but not statistically different from, the survival of patients with T3 N0 M0 disease ($p = 0.07$).

Survival for patients with stage II disease did not otherwise differ on the basis of age older than 70 years ($p = 0.89$), gender ($p = 0.25$), cell type ($p = 0.77$), or adjuvant therapy ($p = 0.37$).

Comments

The purpose of a staging system is to predict survival and, if clinically accurate, to direct therapy. Staging of esophageal carcinoma, however, remains problematic. Previously used staging systems were neither accurate nor predictive and consequently were not widely used. The 1988 revision of the

American Joint Committee on Cancer staging system defined both clinical and pathologic stage by depth of tumor invasion (T), the absence or presence of regional lymph node metastases (N), and the absence or presence of distant metastases (M).⁶ The stage groupings have been arranged to reflect overall prognosis. Patients with stage I carcinomas have a good prognosis, whereas those with stages III and IV carcinoma have a poor prognosis. Stage II includes patients who should have an intermediate survival, but the clinical course of this heterogeneous group has not been well characterized.

Our results suggest that the current classification of stage IIA and stage IIB carcinomas warrants revision. In patients with regional lymph node metastases (N1) the carcinomas behave similarly regardless of the depth of tumor invasion (T1, T2, and T3). Patients who are free of regional lymph node metastases (N0) tended to have a similar survival; however, stratification of these patients by depth of tumor invasion seems to be warranted. Our series is small and a study of larger numbers of these patients, both with and without regional lymph node metastases, may further clarify these relationships.

Our previously reported experience with superficial esophageal carcinomas suggests that the survivals of patients with stage 0 (high-grade dysplasia) and T1 N0 M0 carcinomas confined to the lamina propria or muscularis propria (intramucosal) are similar.⁷ In this study the survival of patients with T1 N0 M0 carcinomas invading the submucosa (submucosal) was significantly worse than that of patients with stage 0 and T1 N0 M0 intramucosal carcinomas. A comparison of patients with T1 N0 M0 submucosal carcinomas and patients with T2 N0 M0 carcinomas demonstrates a similar survival ($p = 0.33$).

Staging is a dynamic process, and it is reasonable to expect a staging system to evolve as understanding of the disease increases. Although the current staging system represents a significant improvement over previous systems, our experience with this system has led us to suggest a reclassification of the staging groups on the basis of survival analysis. Tis N0 M0 and T1 N0 M0 intramucosal carcinomas have a similar behavior and good prognosis.⁷ We consider T1 N0 M0 submucosal and T2 N0 M0 carcinomas to be similar. The trends in survival lead us to consider T3 N0 M0 carcinomas as a separate group. The differentiation of N1 carcinomas by depth of tumor invasion has no clinical relevance, and we consider T1 N1 M0, T2 N1 M0, and T3 N1 M0 carcinomas to have very similar clinical behaviors. Additional studies would be important in confirming these observations.

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Discussion

Dr. Tom R. DeMeester (*Los Angeles, Calif.*). I commend the program committee for selecting this paper for presentation, because the staging of esophageal cancer is indeed an area of controversy. Previous efforts to develop

satisfactory staging criteria have left much to be desired. Two efforts of the American Joint Committee on Cancer, one in 1983 and another in 1988, provide poor discrimination of the stages according to survival.

Dr. Ellis, in a 1993 publication (*J Surg Oncol* 1993;52:231-5), showed, like Dr. Killinger, that the 5-year survival of patients with stage IIA disease was similar to that of patients with stage I disease and the survival of patients with stage IIB disease was similar to that of patients with stage III disease.

Again like Dr. Killinger, he showed that there was no difference between the 5-year survival of patients with T1 or T2 disease (i.e., invasion of submucosa or muscularis propria). Thus two independent institutions and investigators have come to the same conclusion: the current staging system is inadequate. This needs to be corrected for two reasons: First, the current inadequate system supports the bias of oncologists that cancer of the esophagus is a systemic disease from the start and the stage of the disease has a minimal role in decisions regarding therapy; second, the increase in adenocarcinoma of the esophagus and its relation to Barrett's esophagus has identified patients who are at risk for the development of carcinoma and has placed them in surveillance programs. This has resulted in the diagnosis of early disease, at a point at which staging has important therapeutic implications.

Reported experience with resection in patients with early disease by other authors (Skinner et al., *Cancer* 1982;50:2571-5, and Ellis et al., *J Surg Oncol* 1993;52:231-5), like Dr. Killinger's experience, has identified characteristics of esophageal cancer that are associated with improved survival. They are the depth of cancer penetration of the esophageal wall and the presence of lymph node metastasis. These observations have given rise to the W (wall penetration), N (lymph node metastasis), M (systemic organ metastasis) staging system proposed by Skinner and supported by Ellis. It appears that the outcome of Dr. Killinger's study is pointing in the same direction.

On the basis of this background, I have the following questions. First, other investigators have found a difference in survival between tumors that were intramucosal (i.e., limited by the muscularis mucosa), intramural (i.e., limited by the muscularis propria), and transmural (i.e., extending through the esophageal wall. Did you look at your data from this perspective? If so, what were your findings?

Dr. Killinger. Our previously published experience with superficial esophageal carcinoma showed no survival difference between patients with Tis N0 M0, intraepithelial carcinomas and those with T1 N0 M0 carcinomas that did not invade beyond the muscularis mucosae, intramucosal carcinomas. There was a significant survival advantage for these patients with Tis N0 M0 and T1 N0 M0 intramucosal carcinomas compared with those patients with T1 N0 M0 carcinomas that had invaded the submucosa. In the present study, we could find no survival difference between those patients with T1 N0 M0 submucosal tumors and those that have invaded into but not beyond the muscularis mucosa, T2 N0 M0 carcinomas. Survival is worse for those patients with carcinomas that have in-

vaded beyond the muscularis mucosa but not into adjacent structures, T3 N0 M0 carcinomas. Stratification by depth of tumor invasion, T, for carcinomas with regional lymph node metastases, N1, is of no clinical relevance.

Dr. DeMeester. Second, other investigators have found a difference in survival when lymph node metastases were present and when present between patients who had fewer than five nodes and five or more nodes involved. Did you look at your data from this perspective? If so, what was your finding?

Dr. Killinger. We did not quantify the number of lymph nodes that were involved in patients with N1 disease. This is an area that is presently under investigation both prospectively and retrospectively.

Dr. DeMeester. Third, other investigators have suggested that the ratio of involved nodes to the number of total nodes removed has prognostic value, with a ratio of one involved to five uninvolved being beneficial. Did you look at your data from this perspective? If so, what was your finding?

Dr. Killinger. We did not quantify the ratio of involved to total lymph nodes; however, this information is presently being studied.

Dr. DeMeester. I commend you on your efforts to improve the staging of esophageal carcinoma. You have added supporting evidence that there is a need for a change. Ideally, with further accurate data collection by you and others, a new and usable staging system will emerge.

Dr. Arthur N. Thomas (*San Francisco, Calif.*). I have a question and a comment regarding Barrett's esophagus and surveillance. I recently operated on a man who had negative findings 1 year earlier and had what was thought to be a T1-type lesion. However, as Dr. DeMeester has alluded to, he had a single diseased lymph node when the tumor was detected a year later. Thus this patient has a very early tumor and one involved lymph node. Is this the same as T3 disease?

Dr. Killinger. It is my understanding that this patient had a T1 tumor with metastases to regional lymph nodes and no evidence of distant metastases. According to the

present staging criteria, this patient has a T1 N1 M0, stage IIB esophageal carcinoma.

Dr. Thomas. But the end result will be the same as a T3?

Dr. Killinger. Once regional lymph node metastases have occurred there is no need to stratify patients by depth of tumor invasion. This patient has a poor survival outlook because of regional lymph node metastases, regardless of the depth of tumor invasion. The prognosis is worse than that of a patient with a T3 N0 M0 carcinoma.

Dr. John R. Benfield (*Sacramento, Calif.*). I would like to focus on the very vexing problem of local recurrence after esophageal resection. I know that was not the main thrust of your paper, but I notice that you identified some cases and wonder if during your analysis of the data you also elaborated some factors that predispose to local recurrence. I also wonder whether there are any lessons to be learned about preventing this difficult problem.

Dr. Killinger. The data were not analyzed to determine what factors predicted local recurrences.

Dr. Paul F. Waters (*Los Angeles, Calif.*). Were you able to dissect out the role of adjuvant therapy? I noticed you had stratified those patients. Did that have any effect on survival at all?

Dr. Killinger. The survival of patients who received adjuvant therapy was not different from the survival of those treated with resection alone. It must be remembered that a significant number of patients receiving induction therapy were downstaged before resection. Compared with the survival of similar patients with identical pretreatment stage, the survival of these downstaged patients was much improved over the expected survival for their initial clinical stage.

Dr. Waters. Was there any difference in complication rate?

Dr. Killinger. There was no statistical difference in complication rates between those receiving adjuvant therapy and those undergoing resection alone.

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