Geographic Distribution of Regional Metastatic Nodes Affects the Outcome of Trimodality-Eligible Patients with Esophageal Adenocarcinoma

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Key Words

Carcinoma · Chemoradiation · Chemotherapy · Combined modality · Esophageal cancer · Lymph node metastasis · Prognosis · Surgery

Abstract

Background/Aim: Malignant nodes in patients with localized esophageal adenocarcinoma (L-EAC) portend a poor prognosis. We assessed the correlation of the distribution of nodes with the outcome of patients undergoing chemoradiation/surgery (trimodality therapy). **Methods:** We studied 209 L-EAC patients who had confirmed or suspicious nodes at baseline staging. All patients received trimodality therapy and were grouped according to the nodal geography: above the diaphragm (AD), below the diaphragm (BD), or above and below the diaphragm (ABD). Survival estimates were calculated using the Kaplan-Meier method, and the outcomes of the groups were assessed by the log-rank test. **Results:** Patients were primarily Caucasian (91%) and male (93%), with a baseline stage III L-EAC (89%). The me-

dian follow-up was 2.8 years (range, 0.4–11.7). Of the 209 patients, 35% (n = 73) had AD nodes, 20% (n = 41) had BD nodes, and 45% (n = 95) had ABD nodes. ABD patients had a 5-year overall survival rate of 33%, whereas this rate was 55% in AD patients and 60% in BD patients (p = 0.02). Patients with a higher histology grade were also at a higher risk of relapse and had a poor survival (p < 0.01 for both). **Conclusions:** L-EAC patients in the ABD group had the worst outcome after trimodality treatment compared to those in the AD or BD group. Novel strategies are needed for ABD patients.

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Introduction

Therapy of esophageal cancer remains a major challenge because this type of cancer is often diagnosed in advanced stages. In 2014, 18,170 new cases and 15,450 deaths are estimated in the United States [1]. Metastases to regional nodes are frequent and result in a poor 5-year

survival rate of ~21% [2]. With the aid of improved imaging and staging techniques [endoscopic ultrasonography and positron emission tomography (PET)], it has become easier to geographically define the nodal distribution prior to starting therapy [3]. At baseline, malignant nodes can be histologically confirmed by endoscopic ultrasonography and fine needle aspiration (FNA), although this is not always possible [4, 5]. The staging classification also facilitates the designation of nodes in relation to the diaphragm [6]. The literature is rather scant on the prognosis associated with various regional nodal geographies in patients with potentially resectable esophageal carcinoma. We therefore hypothesized that the nodal distribution (above and/or below the diaphragm) will have an influence on patient outcomes, and our focus was on localized esophageal adenocarcinoma (L-EAC) patients who completed chemoradiation followed by surgery (trimodality therapy).

Methods

Patients

We identified L-EAC patients who had pathologically confirmed or suspicious nodes identified at baseline staging from our prospectively maintained database at the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center between 2002 and 2013. Patients with squamous cell carcinoma and those who did not complete trimodality therapy were excluded. No other selection criteria were applied. All patients were fully staged (endoscopic ultrasonography with FNA when needed, PET-CT, and CT scans), and the locations of their nodes were designated before therapy. The clinical stage was assessed according to the American Joint Committee on Cancer (AJCC) manual 6th edition [7]. All patients were discussed in a multidisciplinary conference and divided into 3 groups: above the diaphragm (AD), below the diaphragm (BD), or above and below the diaphragm (ABD). The surgical stage was scored according to the AJCC manual 7th edition based on the evaluation of surgical specimens [8]. The MD Anderson Cancer Center's Institutional Review Board approved this analysis.

Study Design

We retrospectively analyzed the data and calculated overall survival (OS) and relapse-free survival (RFS) for patients in each of the 3 nodal groups.

Treatment

Patients received radiation with chemotherapy consisting of intravenous or oral fluoropyrimidine plus either a platinum compound or a taxane. The radiation therapy dose ranged from 45 to 50.4 Gy delivered in a daily 1.8-Gy fraction. Approximately 6 weeks after the completion of chemoradiation, patients underwent the surgical procedure of the primary surgeon's choice [e.g. trans-thoracic (Ivor-Lewis), transhiatal, total (three-field technique), or minimally invasive procedures].

Surveillance

We surveyed patients as previously described [9]. Follow-up data were garnered from our institution's tumor registry, the hospital records, and the Social Security Database.

Statistical Analysis

Differences in the patient age and length of L-EAC were compared by the Kruskal-Wallis test, whereas differences in other characteristics were analyzed by χ^2 tests (or Fisher's exact test as needed for small sample sizes). Survival curves were estimated using the Kaplan-Meier methods [10]. Univariate and multivariate Cox proportional hazards regression models [11] were used to assess the association between patient characteristics and OS or RFS. Patient characteristics that were significant in the univariate model at the 0.10 level were included in the multivariate model (full model). Then, backward elimination was implemented until all remaining predictors had a p value <0.05 (reduced model). Statistical analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, N.C., USA), and graphics were created in Stata 13.1 (Stata Corp., College Station, Tex., USA).

Results

Patient Characteristics

The patient characteristics are summarized in table 1. Most patients were Caucasian (91%) and male (93%), with a clinical stage III L-EAC (89%). The median follow-up time was 2.8 years (range, 0.4–11.7). At the time of this analysis, 98 (47%) patients had died.

Association between Nodal Groups and Clinical Characteristics

Table 1 shows the patient characteristics by lymph node group. The location of the primary tumor ($p = 0.03$), baseline stage ($p = 0.05$), age ($p = 0.005$), and length of L-EAC ($p = 0.04$) were all significantly associated with the various nodal groups, but this was not the case for histologic grade.

Overall Survival

The median OS was 4.2 years and the 5-year OS rate was 45% (SE = 4). In general, age ($p = 0.004$), tumor grade ($p < 0.001$), and nodal groups ($p = 0.04$) were significantly associated with OS. Older age, higher histologic grade, and ABD nodes were associated with a higher risk of death. The 5-year survival rate was 35% for ABD patients, 49% for AD patients, and 56% for BD patients (HR = 1.70; $p = 0.07$; fig. 1).

In the multivariate analysis, only age and histologic grade, when combined, increased the risk of death by 3% per year of age (HR = 1.03; $p = 0.01$), and patients with poorly differentiated L-EAC were >3 times as likely to die as those with well-to-moderate differentiation (HR = 3.14; $p < 0.001$).

Table 1. Patient characteristics by the location of positive lymph nodes in esophageal cancer patients

Characteristics	Level	All patients (n = 209)	AD patients (n = 73)	BD patients (n = 41)	ABD patients (n = 95)	p value
Age, years		59 [27, 77]	62 [27, 77]	54 [29, 69]	58 [27, 77]	0.005
Gender	Female	15 (7)	5 (6.8)	3 (7.3)	7 (7.4)	>0.99*
	Male	194 (93)	68 (93.2)	38 (92.7)	88 (92.6)	
Race	Non-White	18 (9)	7 (9.6)	3 (7.3)	8 (8.4)	0.95*
	White	191 (91)	66 (90.4)	38 (92.7)	87 (91.6)	
Location of tumor	Esophagus	127 (61)	53 (72.6)	21 (51.2)	53 (55.8)	0.03
	Gastroesophageal junction	82 (39)	20 (27.4)	20 (48.8)	42 (44.2)	
Histologic grade	Well-differentiated	2 (1)	1 (1.4)	0 (0)	1 (1.1)	0.56*
	Moderately differentiated	91 (44)	35 (47.9)	20 (48.8)	36 (37.9)	
	Poorly differentiated	116 (56)	37 (50.7)	21 (51.2)	58 (61.1)	
Tumor length, cm		6.0 [1.5, 17.0]	6.0 [1.5, 12.0]	5.0 [2.0, 12.0]	6.0 [2.0, 17.0]	0.04
Baseline T stage	T2	14 (7)	7 (9.6)	3 (7.3)	4 (4.2)	0.35*
	T3	191 (91)	66 (90.4)	37 (90.2)	88 (92.6)	
	T4	4 (2)	0 (0)	1 (2.4)	3 (3.2)	
Baseline M stage	M0	201 (96)	73 (100)	37 (90.2)	91 (95.8)	0.02*
	M1a	8 (4)	0 (0)	4 (9.8)	4 (4.2)	
Baseline N stage	N1	209 (100)	73 (100)	41 (100)	95 (100)	N/A
Baseline stage	IIB	14 (7)	7 (9.6)	3 (7.3)	4 (4.2)	0.05*
	III	187 (89)	66 (90.4)	34 (82.9)	87 (91.6)	
	IVA	8 (4)	0 (0)	4 (9.8)	4 (4.2)	
Pathologic T stage	pT0	61 (29)	20 (27.4)	10 (24.4)	31 (32.6)	0.77
	pT1	34 (16)	13 (17.8)	6 (14.6)	15 (15.8)	
	pT2	27 (13)	10 (13.7)	8 (19.5)	9 (9.5)	
	pT3+	87 (42)	30 (41.1)	17 (41.5)	40 (42.1)	
Pathologic N stage	pN0	119 (57)	39 (53.4)	27 (65.9)	53 (55.8)	0.69*
	pN1	49 (23)	17 (23.3)	8 (19.5)	24 (25.3)	
	pN2	29 (14)	14 (19.2)	4 (9.8)	11 (11.6)	
	pN3	12 (6)	3 (4.1)	2 (4.9)	7 (7.4)	
Surgical stage	0	48 (23)	17 (23.3)	7 (17.1)	24 (25.3)	0.64
	I	28 (13)	10 (13.7)	6 (14.6)	12 (12.6)	
	II	56 (27)	17 (23.3)	16 (39.0)	23 (24.2)	
	III	64 (31)	26 (35.6)	9 (22.0)	29 (30.5)	
	T0N+	13 (6)	3 (4.1)	3 (7.3)	7 (7.4)	

Values are n (%) or medians [min, max]. * p value for Fisher's exact test.

Relapse-Free Survival

The median RFS was 2.0 years and the 5-year RFS rate was 40% (SE = 4). RFS was significantly associated with age ($p = 0.05$), histologic grade ($p < 0.001$), and nodal group ($p = 0.05$). Patients with ABD nodes had the worst 5-year RFS (33%), followed by AD patients (42%) and BD patients (55%).

Discussion

L-EAC has a high tendency for metastatic progression and probably is a disseminated disease in many patients [12]. One challenge is to identify subsets of trimodality-eligible esophageal cancer patients who are not likely to do well and are likely to have a short survival. Thera-

Fig. 1. Kaplan-Meier OS by the location of positive lymph nodes.

py with considerable morbidity/complication should be avoided in these patients; however, the tools to identify such subsets are quite limited. The basis for this analysis was to examine if nodal distribution could identify a high-risk group. As we suspected, L-EAC patients with ABD nodes fared poorly compared to those with AD or BD nodes. Having defined this, we acknowledge that our results are not sufficient to be implemented in the clinic. However, an alternative treatment strategy should be developed for such high-risk patients.

Our report has the following limitations: (1) retrospective analysis, (2) single-institution experience, (3) relatively small number of patients, and (4) generally limited by the current staging techniques to more accurately designate nodal groups. The strength of the analysis is the novel findings regarding the geographic distribution of nodes.

In conclusion, our data show that patients with ABD nodes fare poorly compared to those with AD or BD nodes.

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Disclosure Statement

The authors have no financial or any other conflict of interest.

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