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ALIMENTARY TRACT

A Model Based on Pathologic Features of Superficial Esophageal Adenocarcinoma Complements Clinical Node Staging in Determining Risk of Metastasis to Lymph Nodes

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BACKGROUND & AIMS: **It is important to identify superficial (T1) gastroesophageal adenocarcinomas (EAC) that are most or least likely to metastasize to lymph nodes, to select appropriate therapy. We aimed to develop a risk stratification model for metastasis of superficial EAC to lymph nodes using pathologic features of the primary tumor.**

METHODS: **We collected pathology data from 210 patients with T1 EAC who underwent esophagectomy from 1996 through 2012 on factors associated with metastasis to lymph nodes (tumor size, grade, angiolymphatic invasion, and submucosal invasion). Using these variables, we developed a multivariable logistic model to generate 4 categories for estimated risk of metastasis (<5% risk, 5%–10% risk, 15%–20% risk, or >20% risk). The model was validated in a separate cohort of 39 patients who underwent endoscopic resection of superficial EAC and subsequent esophagectomy, with node stage analysis.**

RESULTS: **We developed a model based on 4 pathologic factors that determined risk of metastasis to range from 2.9% to 60% for patients in the first cohort. In the endoscopic resection validation cohort, higher risk scores were associated with increased detection of lymph node metastases at esophagectomy ($P = .021$). Among patients in the first cohort who did not have lymph node metastases detected before surgery (cN0), those with high risk scores (>20% risk) had 11-fold greater odds for having lymph node metastases at esophagectomy compared with patients with low risk scores (95% confidence interval, 2.3–52 fold). Increasing risk scores were associated with reduced patient survival time ($P < .001$) and shorter time to tumor recurrence ($P < .001$). Patients without lymph node metastases (pT1N0) but high risk scores had reduced times of survival ($P < .001$) and time to tumor recurrence ($P = .001$) after esophagectomy than patients with pT1N0 tumors and lower risk scores.**

CONCLUSIONS: **Pathologic features of primary superficial EACs can be used, along with the conventional node staging system, to identify patients at low risk for metastasis, who can undergo endoscopic resection, or at high risk, who may benefit from induction or adjuvant therapy.**

Keywords: Prognostic; Lymphatic Invasion; Tumor Budding; Tumor Grade; Submucosal Invasion.

In most patients, surgically resected, superficial (T1) adenocarcinoma of the esophagus or gastroesophageal junction (EAC) has a favorable survival outcome relative to more deeply invasive cancers.[1] However, despite tumor that is confined to the mucosal or submucosal layers, up to 16% of patients with T1 EAC have nodal metastases identified at surgical resection.[2–7] These patients have significantly worse prognosis.[3,8] Currently, decisions for therapeutic intervention are based primarily on estimation of risk for nodal metastasis using depth of tumor invasion and clinical assessment of nodal stage. For patients with T1 cancers thought to have minimal risk of nodal metastases, many centers are advocating endoscopic resection (ER) alone,

Abbreviations used in this paper: ALI, angiolymphatic invasion; CT, computed tomography; EAC, esophageal adenocarcinoma; ER, endoscopic resection; EUS, endoscopic ultrasound; PET, positron emission tomography.

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or less extensive nodal dissection during esophagectomy. Conversely, patients thought to have nodal metastasis based on clinical staging are often referred for induction chemoradiotherapy. Unfortunately, endoscopic ultrasound (EUS), although more sensitive than either computed tomography (CT) or 18F-fluoro-2-deoxy-D-glucose positron emission tomography (PET), is only 70%–80% sensitive and specific for nodal metastasis.[9] Complementary methods must be used to accurately estimate the likelihood of nodal metastases.

Based on a widespread consensus in the literature,[2–7,10–14] submucosal invasion is routinely evaluated by staging ER of superficial EAC and is regarded as the paramount risk factor for nodal metastasis.[15] However, we and others have identified additional histopathologic risk factors for nodal metastasis, including angiolymphatic invasion (ALI),[5,6,11,13–17] higher grade,[4–6,11,14,15,17] tumor budding,[17] and larger tumor size.[5,11,13,15,17] It is standard practice for pathologists to report some or all of these findings in preoperative staging ER specimens. Hence, in practice, clinicians must decide how best to treat tumors with knowledge of all of these characteristics. Despite the widely held belief that invasion into the submucosa is a "watershed" for nodal metastasis,[15] there seems to be a trend toward the treatment of intramucosal and submucosally invasive adenocarcinomas by ER.[18] This may be because of other clinical considerations (eg, patient age and comorbidities) or the perception that it is possible to identify submucosal cancers with an acceptably low risk of nodal metastasis.[19]

The central aim of this study is to develop a quantitative model of the probability of nodal metastasis based on rigorously defined, known pathologic risk factors and evaluate how it may complement current methods of risk stratification based on clinical node staging. We also sought to determine whether the presence of histopathologic risk factors in the primary tumor would be associated with survival outcome, particularly in cases pathologically staged as node negative (pT1N0) that are unlikely to receive adjuvant treatment.

Methods

Patient/Case Selection

This study was approved by the University of Pittsburgh Institutional Review Board with waiver of consent. We reviewed all patients with superficial (T1) EAC recorded who underwent esophagectomy from 1996 to 2012. Patients with high-grade dysplasia only, patients initially treated by ER, and patients who received neoadjuvant therapy were excluded. The cases included in this study have been previously reported.[17] The electronic medical record and physical charts were reviewed for patient and treatment variables. Preoperative clinical stage was assigned based on radiographic findings (including available CT, PET, and/or PET/CT scans) and EUS examination.

A total of 210 patients had representative slides available for detailed histopathologic review. Without knowledge of the pathologic lymph node stage, all available diagnostic hematoxylin and eosin stained slides representing the primary tumor were reviewed by the authors (MSL and JMD) to score the following pathologic features of the primary tumor: depth of invasion, tumor grade, ALI, and tumor size (scoring criteria are summarized in Table 1 as previously described[17]). The final classification of each variable was based on the consensus diagnosis of the 2 pathologists. After scoring these pathologic features, the originally reported lymph node stage was confirmed on histologic review.

Table 1. Scoring Histopathologic Risk Factors for Nodal Metastasis

Risk factor	Classification or measurement criteria[a]
Depth of invasion	
Intramucosal (T1a)	EAC invading no deeper than the true muscularis mucosae
Superficial T1a	EAC confined to the lamina propria
Deep T1a	EAC invading any layer of the muscularis mucosae (duplicated or true)
Submucosal (T1b)	EAC invading into the submucosa
Superficial T1b	EAC invading no deeper than the upper half of the submucosa, assessed at the deepest point of invasion
Deep T1b	EAC invading into the lower half of the submucosa, assessed at the deepest point of invasion
Histologic grade	
Low grade	Well or moderately differentiated (>50% tubular, papillary, or gland forming; based on all tumor sections) AND no more than focal tumor budding
High grade	Poorly differentiated (<50% tubular, papillary, or gland forming; based on all tumor sections) OR extensive tumor budding
Angiolymphatic invasion	
Present	Unequivocal evidence of tumor epithelial cells within endothelium-lined vascular space
Absent	Above criterion not met
Tumor size	Tumor size (in cm) based on maximal cross-sectional dimension on histologic sections or maximal gross tumor size measurement; for multifocal tumors, size of the largest focus was used; tumors were then classified as <2 cm or ≥2 cm

[a]As previously described in Landau et al.[17]