



cT2N0 esophageal adenocarcinoma: predictors of lymph nodal involvement and clinical significance

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American Joint Committee on Cancer (AJCC) classifies esophageal adenocarcinoma (EAC) into different T stages according to the depth of tumor infiltration. The treatment is stage dependent and has historically been associated with a dismal 5-year overall survival of ~10% for tumors crossing the submucosa. Early stage EAC includes tumor invasion to mucosal layers and without metastasis to nodes or other tissues (TisN0M0, T1aN0M0) while the terminology “superficial cancers” is reserved for tumors limited to the submucosa (T1bN0M0).

Squamous cell carcinoma (SCC) and EAC differ in their etiology, tumor biology, tumor location, and long-term outcomes. In superficial esophageal cancer cases, EAC carries a lower risk of lymph node metastasis than SCC, which is more locoregional. Regardless, EAC are frequently associated with lymph nodal involvement, either detected pre-operatively or on histopathology. The prevalence lymph node involvement increases with increasing T stage. Prevalence of lymph nodal metastases or lymphatic involvement by tumor can be seen in up to 7% patients with T1a EAC while almost half of the patients may have lymphatics involved and 20% have lymph nodal involvement once the tumor reaches the submucosa (T1b) (1-3). Lorenz and colleagues identified lymph node involvement as the sole prognostic indicator for the survival and disease recurrence (4). While T stage showed a correlation with the possibility of lymph nodal involvement, they could not determine a clear cut-off of tumor infiltration into the esophageal wall that would confer insignificant risk of lymph nodal involvement. In a landmark study

Siewert *et al.* in 2001, showed that carcinoma esophagus has more than 70% lymph nodal metastasis in T2 disease irrespective of the histology (5). It is a common consensus that preoperatively diagnosed T2N0M0 lesions (tumor infiltrating muscularis propria) are found to involve lymph node metastasis when the resected specimens are examined.

Whilst there are ongoing discussions on the impact of routine lymph node dissection on survival in all cases, it is accepted that lymphadenectomy enables proper staging and prognostication and despite lack of high-quality scientific data, it is believed to improve disease-free survival by most surgeons. Patients with clinical evidence of node-negative T1 EAC are treated by R0 resection of the lesion, either through surgical or endoscopic approach without neoadjuvant therapy (6). On the other hand, locally advanced disease, i.e., T3 lesion or node-positive patients, receive induction chemoradiotherapy followed by radical surgical resection. In a patient undergoing resection alone, the presence of node positivity on histopathology confers a poor prognosis (4). Controversially, surgery first approach with limited lymphadenectomy for the clinical T2N0 disease is considered by many authors as insufficient, and in our experience, these patients tend to have a high recurrence rate at long-term follow-up. Various RCTs have shown that in T2N0 esophageal carcinoma, multimodal therapy is the treatment of choice irrespective of the postoperative pathologic staging (7). The number of patients specific to the T2N0 stage in such trials is too small to be able to draw any inferences or recommendations for the treatment guidelines.

Endoscopic ultrasound (EUS) has long been considered the gold standard for staging of non-metastatic early esophageal cancer with reported sensitivity to detect regional lymph node involvement of almost 80% as compared with other imaging modalities such as computed tomography (CT) (50%) and fluorodeoxyglucose positron emission tomography (FDG-PET) (57%) (8). Hallmarks of a suspicious node on EUS include, but are not limited to, central necrosis, hypo-echogenicity, round to oval shape, are infrequently enlarged in size and usually maintain clear planes from other mediastinal structures. EUS guided fine needle aspiration (FNA) increases sensitivity but is limited by inadequate tissue sampling. With advancement in technology, the accuracy of EUS has increased in detecting locally advanced cancer (T3N1–3 disease), however, its sensitivity is still debatable for early staged lesions, with its propensity to overstage the disease (9,10). Despite the central role of EUS in lymph nodal staging, several studies have reported a high prevalence of lymph nodal metastases in T1 and T2 disease frequently underestimated by EUS. It has been reported that staging by EUS and limited lymphadenectomy underestimates actual lymph nodal metastatic load (3). Further, lymph node size is a non-specific marker for cN status. Approximately 10–20% of normal-sized nodes may contain metastatic deposits, and metastatic nodes in direct contact with the tumor may be indistinguishable from the primary tumor (11). Role of endoscopic therapies for early-stage esophageal cancer [endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD)], especially T1 disease (limited to mucosa and submucosa), despite advantages of organ preservation and least morbidity and mortality, is debated by many authors in view of the possibility of lymph nodal metastases. Although adjuvant therapies are employed to treat possible micro-metastases and lymph nodal involvement, the role of endoscopic therapies is much limited and radical surgical resection remains the gold-standard treatment (3). The reported rates of recurrence and lymph nodal involvement in clinically node-negative tumors make it difficult justify the use of local therapies or endoscopic resections without regional lymphadenectomy. Surgical resection is associated with significant morbidity and mortality and a substantial impact on quality of life of the patient (12). Employing minimally invasive approach (endoscopic resection of the mucosal or submucosal tumors) would be desirable in a selected subgroup of patients, could preoperative predictive markers be identified which can stratify early-stage EAC patients into those with or without

lymph nodal metastasis with acceptable accuracy.

The recent study “Predictors of Nodal Metastases for Clinical T2N0 EAC” by Barbetta and colleagues at MSKCC, NY, USA refutes the notion of EUS being the accurate modality for identification of the nodal involvement (13). In this novel study of 80 patients with clinically T2N0 EAC who were treated with surgery with or without adjuvant chemotherapy, preoperative staging by EUS was found to be inaccurate in 91% of the patients. They further employed logistic regression to identify risk factors associated with lymph nodal involvement.

The study included 80 patients who received curative surgery with or without adjuvant therapy. All included patients were cT2N0 according to preoperative EUS staging. Post resection, 73/80 patients were found to be inaccurately staged, which included 40 patients (50%) who were preoperatively overstaged and 33 patients (41%) preoperatively understaged. Node positivity was found in 35% patients (n=28), however, Orringer approach only yielded a limited lymphadenectomy with a median of 8 lymph nodes (*vs.* 24 and 27 with Ivor-Lewis and McKeown approaches respectively). PET was employed for pre-operative staging in 72 patients (90%) and showed a higher uptake (not statistically significant) in node-positive patients. Using logistic regression, the study found vascular invasion and neural invasion as the risk factors, with vascular invasion being the independent predictor of pathologic nodal involvement. The authors did not find any significant correlation of nodal involvement with primary tumor characteristics including size, location, and grade. Further, patients with nodal involvement had poorer long-term survival.

A research group from China, in their retrospective analysis of 93 cases of superficial esophageal carcinoma, reported the depth of invasion and degree of differentiation to significantly correlate with lymph nodal involvement (14). They emphasized the need for close follow up following endoscopic resection in m3 and sm1 diseases and considered surgical resection to be the treatment of choice for sm2 disease and above, which restated the stand that adequate lymphadenectomy is needed for complete clearance of the occult disease. In this study, with tumor diameter exceeding 3 cm, infiltration into submucosa and the lymph node involvement rate was high. Patients with lymphovascular invasion had significantly higher Lymph node metastasis than in patients without it (32.1% *vs.* 4.6%) (14).

A study from Germany by Dubecz *et al.*, one of the earliest studies discussing early stage cancers in a

large sample size of 1,200 patients, infiltration into the submucosa, tumor size more than 10 mm, and poor tumor differentiation were independently associated with the risk of nodal disease (3). More than 20% of patients with these risk factors had lymph nodal metastases, which further translated into a poorer 5-year overall survival in the EAC group (but not in the squamous group). Rice *et al.* in their analysis of 5,806 patients, found that the depth of wall invasion, the length of esophageal segment invaded by tumor, and grade were associated with an increasing number of positive nodes (15). This study stated an inverse relationship between the grade of tumor and the minimum number of nodes needed to be dissected to adequately determine N status. The study, however, didn't include patients undergoing multimodality treatment, which is the current standard of care for carcinoma esophagus.

Another important factor which needs discussion is occult lymph node microscopic metastasis (OLNMM), which is frequently missed despite extensive preoperative workup and adds on to the poor prognosis of the disease in spite of lymphadenectomy. Studies have shown a prevalence of up to 10–50% of OLNMM in early stage N0 specimens (16). Meticulous evaluation of the cells in the lymph nodes with advanced staining and immunohistochemical techniques can increase the yield. Whether these expensive and time-consuming techniques are really necessary is still controversial (17). A retrospective study by Mayo clinic on OLNMM as a predictor of lymph node relapse in node-negative patients found no association between OLNMM and cancer relapse, and thus routine immunohistochemistry was not advocated in pN0 disease (18). Sentinel lymph node sampling is a novel concept in gastrointestinal cancers which theoretically may spare unnecessary lymph node dissection, while maintaining R0 resection and improving target lymph node yield, however, this concept is still in its nascent stages and needs further focused research (19).

From the point of view of improving the diseases free survival for the patient, however, we believe that overstaging the disease is a more acceptable alternative to employing invasive investigations such diagnostic endoscopic resection and thoracoscopy to accurately stage the disease. Identifying preoperative markers which can predict nodal and/or lymphatic involvement in an early staged EAC are highly desirable. Using univariate and multivariate analyses of their patient data, several studies have determined possible determinants of nodal involvement in early EAC. Most of these studies are limited by retrospective nature, inadequate sample size, and wide heterogeneity. Further, the specificity

of these markers needs to be determined through a multicentric, prospective, large sample study. Endoscopic resection as a diagnostic modality along with careful staging using a multitude of EUS, PET-CT, and elective thoroscopic sampling may be employed to determine the patients who are candidates of an organ-preserving procedure. Barbetta and colleagues, through their study, have emphasized the need of identifying and stratifying such markers which may help avoid morbid resection in a select subset of patients (13). The study is a descriptive study, a retrospective review of the prospectively maintained database. We maintain an extensive prospective database at our center and such databases diminish the possibility of recall bias typically associated with the retrospective studies.

In conclusion, the depth of invasion, tumor differentiation, tumor size, and lymphovascular infiltration were closely associated with lymph node metastasis, and the depths of invasion and lymphovascular invasion were independent risk factors of lymph node metastasis in T2N0 carcinoma esophagus. To make a choice between surgery or chemotherapy alone versus combination therapy we need large sample size which is very difficult in this subset of patients which have a very high likelihood of lymph nodal metastasis irrespective of the prognostic factors described above. Decision making in the therapy of patients with T2N0 tumors should be individualized according to the patient's overall status, the presence of comorbidities, and histopathologic variables of the tumor. Multimodality treatment would be appropriate for these patients with T2N0 EAC patients based on current evidence till such predictors of lymph nodal metastases are firmly established to be safely utilized in the clinical decision making. Further research on such predictive markers is highly desirable.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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