Review Article

Management of clinical T2N0 esophageal cancer: a review

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Contributions: (I) Conception and design: TJ Birdas; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: While management of locally advanced esophageal cancer has mostly involved multimodality therapy, management of clinical T2N0 patients has been more controversial, primarily as a result of inaccurate clinical staging with existing modalities. This review article examines current literature on this topic and provides recommendations for management of individual patients.

Keywords: Esophageal cancer; esophagectomy; neoadjuvant therapy

Submitted Jul 23, 2019. Accepted for publication Jul 25, 2019.
doi: 10.21037/jtd.2019.07.85
View this article at: http://dx.doi.org/10.21037/jtd.2019.07.85

Esophageal adenocarcinoma has become more prevalent in the US, with a 16-fold increase over the course of the second half of the twentieth century. This pathology can be a devastating disease, with 5-year survival reported as low as 14%. When stratifying patients, the most important prognostic factors are preoperative clinical stage and the presence of nodal metastasis (Dolan). Because of the significant morbidity associated, interest in the development of appropriate treatment is certainly high. Resection has been the mainstay of treatment, but management choices have evolved, with continued discussion of the role of neoadjuvant therapy (chemotherapy or chemoradiotherapy), endoscopic interventions, and adjuvant therapy. Data conflict, but there is some consensus on the role of neoadjuvant chemoradiotherapy (CRT) followed by resection in T3 disease and N1 or greater disease (1). Treatment is grounded in the acceptance that pathologic complete response improves survival (2).

In addition to the role of neoadjuvant therapy for locally advanced disease, general agreement exists on the effectiveness of resection for early stage T1 disease (the debate focusing on the appropriate role for endoscopic resection compared to surgical therapy). Clinical T2N0 (cT2N0) disease, however, is a controversial subset of patients within the larger population of patients with esophageal cancer (1). T2 disease invades the muscularis propria of the esophagus, with potential infiltration into submucosal lymphatics, but is confined to the walls of the esophagus (1,3,4). It is, thus, considered to be an intermediate and therefore unpredictable tumor group. Taken as a whole, clinical T2N0 5-year survival hovers around 50% (4). The approach to cT2N0 disease becomes rather difficult, in no small part because clinical staging is often unreliable. Studies have shown that at time of resection, upstaging of cT2N0 patients is a fairly common occurrence. Our own 21-year institutional experience found a 48.5% rate of understaging in patients who underwent surgery. This was more common in poorly differentiated tumors (5). This is supported by the literature, with other studies citing 25–55% of these patients upstaged, and 35% found to have positive lymph nodes (6,7). This is not an insignificant finding, as the finding of positive nodes in this patient group led to poor survival (41% at 5-year follow-up) (6). Upstaging has been found to increase in frequency with poor differentiation, lymphovascular invasion and higher tumor size (over 3 cm) (8-10).

Histology of carcinoma is another aspect of esophageal disease that must be explored. While adenocarcinoma is the most common type in the US and Western Europe, squamous cell carcinoma also makes up a portion of disease.

Squamous cell carcinoma has been found to have higher rates of pathologic complete response when patients are treated with adjuvant and neoadjuvant chemoradiotherapy (11). Differences in this patient group are present in origin cell type, but there are also differences in the epidemiology and, because the geography differs, health care systems differences in availability of care. Thus, discussion on the approach to cT2N0 disease cannot be generalized from adenocarcinoma to squamous cell carcinoma (8).

The controversy in treatment is multifold, and optimal treatment has yet to be defined (4). Part of the difficulty in the development of evidence-based recommendations is that prior randomized controlled trials have either been too limited in scope, had inaccurate preoperative staging, or lacked sufficient subgroup analysis (2).

Staging

Despite a lack of clear guidelines for the treatment of this patient population, there are at least fairly standard accepted aspects of the preoperative testing of these patients. In order to stage before surgical resection, most patients undergo CT scan of the chest, abdomen, and pelvis, FDG-PET scan, and EUS evaluation (1). Each of these tests, while certainly crucial, carries with it some degree of error and, thus, the opportunity for contributing to error in staging. Accurate clinical staging directs care but is difficult to obtain, and pathological staging has been found to differ from clinical staging in as much as 90% of cases (5,9,12,13).

CT scanning is excellent for obtaining the largest amount of detail of the general state of the tumor. Specifically, depth of invasion can be evaluated through this modality, and nodal involvement assessed. Unfortunately, the accuracy of CT scanning for measurement of depth of invasion is cited as 50–80%, and nodal involvement is accurate in 50–70% (1,2). The value of FDG-PET is in the detection of radio uptake seen in malignant cells, with the goal of metastatic detection. The sensitivity and specificity of PET scanning for regional metastases, however, ranges from 57–85% (1,2). EUS allows for evaluation of depth of invasion, regional nodes, and lymphovascular invasion. Lymphovascular invasion is an area of interest because it is the only independent predictor of the presence of nodal involvement in a study of tumor variables (odds ratio 5.24) (6). EUS accuracy for the detection of regional nodes stands at 80%, and at 74–90% for the evaluation of T stage in all esophageal cancer patients, but the accuracy of T stage evaluation is lowest in T2 tumors, with accurate description of 31% (1). Interestingly, despite advances in the technology supporting each of these modalities, the accuracy of staging has not improved in recent years (14).

Treatment

When considering the treatment options for cT2N0 disease, the main area of contention is on the role of neoadjuvant chemoradiotherapy prior to surgical resection. It should be briefly mentioned that endoscopic resection has been explored in one study in this patent group (15), reflecting the frequent overstaging of cT2N0 patients. This approach has not been adopted widely, and most cT2N0 patients will receive more radical treatment.

The volume of studies examining the role of multimodality therapy is not as broad as that for other clinical stages. In our previously reported experience, we found that among patients who underwent induction therapy the pathologic complete response rate was 27.2%; patients who received this therapy were less likely to have lymph node metastasis at resection (12.1% *vs.* 40%) although long-term survival was similar (5). A recent systematic review of ten studies comparing neoadjuvant therapy with surgery alone in clinical T2N0 found no improvement in survival with neoadjuvant therapy, no difference in recurrence risk, no difference in anastomotic leak rates, and actually demonstrated a lower probability for R0 resection in patients who received induction therapy (4). Markar *et al.* examined a cohort of 2,944 patients with cT2N0 disease and found no survival benefit or decreased recurrence in patients who received neoadjuvant therapy. The only difference found was a greater rate of malnutrition in the patients receiving neoadjuvant therapy (21.4% *vs.* 9.8% in the surgery group). Nodal understaging was widespread, and this group had a median 1.7 positive lymph nodes at time of resection, with 48.1% understaged for nodal status, and 34.7% understaged for T status (7). The Esophageal Cancer Study Group examined data on clinical T2N0 patients from twenty-six high volume centers, fifteen of which contributed original data (14). They found a median survival of 57% at 5 years, without differences across patients receiving induction therapy and surgery. This was in the setting of pathologic complete response in 29% of patients receiving induction CRT. Staging was accurate in only 14% of patients, with 50% of patients understaged, including 39% who were found to be node-positive. A review of all cT2N0 patients between 1998 and 2011 in the National Cancer Database revealed similar

outcomes, with a similar survival in the group receiving esophagectomy alone and patients with induction therapy [41.1 *vs.* 41.9 months (16)]. Finally, specifically considering squamous cell carcinoma, Chen's group found that patients who received neoadjuvant CRT were able to achieve pathologic complete response in 37% of cases. Still, this did not result in improved overall survival compared to surgery alone but did improve disease specific survival (85% at 5 years with pathologic complete response followed by esophagectomy (3).

Contrary to these studies, a study of 533 patients from the Netherlands Cancer Registry identified both a higher rate of radical resection and better long-term survival in the neoadjuvant group (17). It thus appears that the overwhelming majority of current literature, although retrospective, points towards a lack of clear benefit of neoadjuvant therapy in cT2N0 patients. This is especially important given that the use of CRT is not totally benign and could increase risk of postoperative complications (4,16,18).

The question of who receives neoadjuvant therapy was considered by Samson *et al.* (19). They considered factors associated with induction therapy. Higher education, receiving treatment at a community cancer center, and more recent diagnosis year all were associated with significantly higher rates of neoadjuvant treatment. The only factor they found to decrease likelihood was increased age. The results of this study certainly raise socioeconomic questions and are worthy of further consideration.

The timing of neoadjuvant therapy prior to esophagectomy has also been explored. Qin *et al.* conducted a review of twelve studies, with a focus on if surgery conducted farther than 7 to 8 weeks after the completion of CRT had an impact on treatment (20). They found that in patients who received esophagectomy less than 7 weeks after CRT had higher rates of pathologic complete response. Additionally, 30-day mortality was increased in patients who had a longer period between CRT and surgery. This result was explored further and found to be significant in the subgroup of patients with adenocarcinoma, while patients with squamous cell carcinoma had similar outcomes regardless of timing.

Conclusions

The approach to cT2N0 esophageal cancer is a complex and controversial one. Inconsistency in preoperative staging, flaws in diagnostic instruments, and absence of large randomized controlled trials lead to a dearth of clear guidelines for these patients. NCCN recommendations are upfront surgery with low-risk lesions, but CRT, chemotherapy, or definitive chemoradiation for all others (9), but these recommendations leave a great deal of discretion to individual providers. While the majority of studies have not demonstrated benefit to survival with CRT, subgroup analysis of understaged patients who receive treatment has not yet been adequately explored. With discordant staging, patients who are overstaged and thus overtreated are included with those patients whose nodal status in underpredicted, which could certainly bias results. Unfortunately, until a study with large enough subgroups to explore these effects is conducted, it is difficult to quantify these effects. Improving the accuracy of preoperative testing and consequently preoperative staging should be of the highest priority when considering the future direction of treatment for cT2N0 esophageal cancer, and multicenter studies of this patient population can provide the data necessary to make a meaningful recommendation for this patient group.

At this point in time, recommendations should be that patients with cT2N0 esophageal cancer should undergo the most accurate pre-treatment staging possible before decision-making for the use of neoadjuvant therapy. It is also important to keep in mind the risk factors for upstaging as identified in several studies, including presence of lymphovascular invasion, poor tumor differentiation and tumor size >3 cm when deciding how to proceed with patient treatment. It seems reasonable to consider neoadjuvant therapy when one or more of these factors are present; as there is no set pathway for approach to cT2N0 disease, each patient's treatment algorithm will be somewhat unique, and it is up to the provider to make the choices that are best for each patient.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

References

1. Sancheti M, Fernandez F. Management of T2 esophageal cancer. Surg Clin North Am 2012;92:1169-78.
2. Dolan JP, Kaur T, Diggs BS, et al. Significant understaging is seen in clinically staged T2N0 esophageal cancer patients undergoing esophagectomy. Dis Esophagus 2016;29:320-5.
3. Chen WH, Chao YK, Chang HK, et al. Long-term outcomes following neoadjuvant chemoradiotherapy in patients with clinical T2N0 esophageal squamous cell carcinoma. Dis Esophagus 2012;25:250-5.
4. Mota FC, Cecconello I, Takeda FR, et al. Neoadjuvant therapy or upfront surgery? A systematic review and meta-analysis of T2N0 esophageal cancer treatment options. Int J Surg 2018;54:176-81.
5. Hardacker TJ, Ceppa D, Okereke I, et al. Treatment of clinical T2N0M0 esophageal cancer. Ann Surg Oncol 2014;21:3739-43.
6. Barbetta A, Schlottmann F, Nobel T, et al. Predictors of Nodal Metastases for Clinical T2N0 Esophageal Adenocarcinoma. Ann Thorac Surg 2018;106:172-7.
7. Markar SR, Gronnier C, Pasquer A, et al. Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study. Eur J Cancer 2016;56:59-68.
8. Kidane B, Korst RJ, Weksler B, et al. Neoadjuvant therapy versus upfront surgery for clinical T2N0 esophageal cancer: A systematic review. Ann Thorac Surg 2019. [Epub ahead of print].
9. Shridhar R, Huston J, Meredith KL. Accuracy of endoscopic ultrasound staging for T2N0 esophageal cancer: a National Cancer Database analysis. J Gastrointest Oncol 2018;9:887-93.
10. Semenkovich TR, Panni RZ, Hudson JL, et al. Comparative effectiveness of upfront esophagectomy versus induction chemoradiation in clinical stage T2N0 esophageal cancer: A decision analysis. J Thorac Cardiovasc Surg 2018;155:2221-30.e1.
11. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246:363-72; discussion 372-4.
12. Shin S, Kim HK, Choi YS, et al. Clinical stage T1-T2N0M0 oesophageal cancer: accuracy of clinical staging and predictive factors for lymph node metastasis. Eur J Cardiothorac Surg 2014;46:274-9; discussion 279.
13. Crabtree TD, Kosinski AS, Puri V, et al. Evaluation of the reliability of clinical staging of T2 N0 esophageal cancer: a review of the Society of Thoracic Surgeons database. Ann Thorac Surg 2013;96:382-90.
14. Atay SM, Correa A, Hofstetter WL, et al. Predictors of staging accuracy, pathologic nodal involvement, and overall survival for cT2N0 carcinoma of the esophagus. J Thorac Cardiovasc Surg 2019;157:1264-72.e6.
15. Gotink AW, Spaander MC, Doukas M, et al. Exploring diagnostic and therapeutic implications of endoscopic mucosal resection in EUS-staged T2 esophageal adenocarcinoma. Endoscopy 2017;49:941-8.
16. Speicher PJ, Ganapathi AM, Englum BR, et al. Induction therapy does not improve survival for clinical stage T2N0 esophageal cancer. J Thorac Oncol 2014;9:1195-201.
17. Goense L, Visser E, Haj Mohammad N, et al. Role of neoadjuvant chemoradiotherapy in clinical T2N0M0 esophageal cancer: A population-based cohort study. Eur J Surg Oncol 2018;44:620-5.
18. Rice TW, Mason DP, Murthy SC, et al. T2N0M0 esophageal cancer. J Thorac Cardiovasc Surg 2007;133:317-24.
19. Samson P, Puri V, Robinson C, et al. Clinical T2N0 Esophageal Cancer: Identifying Pretreatment Characteristics Associated With Pathologic Upstaging and the Potential Role for Induction Therapy. Ann Thorac Surg 2016;101:2102-11.
20. Qin Q, Xu H, Liu J, et al. Does timing of esophagectomy following neoadjuvant chemoradiation affect outcomes? A meta-analysis. Int J Surg 2018;59:11-8.

Cite this article as: Vining P, Birdas TJ. Management of clinical T2N0 esophageal cancer: a review. J Thorac Dis 2019;11(Suppl 12):S1629-S1632. doi: 10.21037/jtd.2019.07.85

