Accuracy of endoscopic ultrasound staging for T2N0 esophageal cancer: a National Cancer Database analysis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: To determine accuracy of clinical staging of T2N0 esophageal cancer from the National Cancer Database (NCDB).

Methods: The NCDB was accessed to identify patients with T2N0M0 esophageal cancer (adenocarcinoma or squamous cell carcinoma) treated between 2004–2013 that underwent esophagectomy. Pathologic staging was compared to clinical stage. Univariate (UVA) and multivariate analysis (MVA) was performed to identify factors related to pathologic upstaging using Cox proportional hazard ratio.

Results: We identified 1,840 patients with T2N0 esophageal cancer who underwent esophagectomy as first line therapy. The median age was 67 years. The vast majority of patients were male and had distal adenocarcinomas. Clinical staging in was accurate pathologically in 30.7% of patients. While there was a trend for worse accuracy with increasing year of diagnosis, there rate of pT0–2N0 was stable. Tumor length >3 cm was significantly associated with tumor upstaging, while poor differentiation was significantly associated with nodal upstaging. UVA and MVA identified younger age, tumor length >3 cm, and poor differentiation were significantly associated with overall upstaging. Gender, tumor location, and tumor histology were not prognostic.

Conclusions: Clinical staging for T2N0M0 esophageal cancer continues to remain highly inaccurate, however, rates of pT0–2N0 have steadily remained over 50%. Tumor length >3 cm and poor differentiation are strongly associated with pathologic upstaging.

Keywords: Esophageal cancer; T2N0; staging; National Cancer Database (NCDB)

Submitted Dec 15, 2017. Accepted for publication Jan 16, 2018.
doi: 10.21037/jgo.2018.01.16
View this article at: http://dx.doi.org/10.21037/jgo.2018.01.16

Introduction

In 2017, there will be 16,940 new cases of esophageal cancer diagnosed, with 15,690 dying from the disease in the United States (1). The majority of esophageal cancers are either adenocarcinoma or squamous cell carcinoma. Trimodality therapy of neoadjuvant chemoradiation followed by surgical resection has been established as the standard of care for advanced disease (2,3). However, the role of multimodality therapy in the management of clinical T2N0 esophageal cancer remains controversial. The NCCN recommends upfront surgery for T2N0 esophageal cancers if lesions are low-risk (well differentiated, <2 cm), but recommends either preoperative chemotherapy, preoperative chemoradiation, or definitive chemoradiation for all others (4).

Several issues arise when considering management of clinical T2N0 esophageal cancers including mostly retrospective studies with small sample size and earlier time periods, inclusion of both squamous cell carcinoma of adenocarcinoma patients, inclusion of patients treated with multiple types of induction therapy with either

Table 1 Patient characteristics

Variable	N (%) [1,840]
Median age, years [range],	67 [22–90]
Gender	
M	1,479 (80.4)
F	361 (19.6)
Location	
Middle	156 (8.5)
Lower	760 (41.3)
GEJ	885 (48.1)
Overlap	39 (2.1)
Histology	
Adenocarcinoma	1,610 (87.5)
Squamous cell	230 (12.5)
Median tumor length, cm (range)	3.0 (2.0–4.2)
Path T stage	
T0	24 (1.3)
T1	538 (29.2)
T2	802 (43.6)
T3	461 (25.1)
T4	15 (0.8)
Path N stage	
N0	1,209 (65.7)
N1	478 (26.0)
N2	101 (5.5)
N3	52 (2.8)
Median lymph nodes removed [range]	14 [8–21]
Grade	
Well	149 (8.1)
Moderate	777 (42.2)
Poor	914 (49.7)
Surgical margins	
No residual	1,677 (91.1)
Microscopic	160 (8.7)
Macroscopic	3 (0.2)
Facility volume	
Low (<10/year)	1,081 (58.8)
Medium (10–20/year)	401 (21.8)
High (>20/year)	358 (19.5)

GEJ, gastroesophageal junction.

chemotherapy, chemoradiation, or radiation therapy, and no reporting of outcomes of patients treated with definitive chemoradiation (5-10). A recent randomized study failed to show a survival benefit of neoadjuvant therapy in stages I and II esophageal cancer patient, however, 70% of patients had squamous cell carcinomas (11).

While clinical T2N0 esophageal cancer is considered early stage, several reports have documented significant tumor and nodal understaging in >50% of patients not receiving induction therapy (6,12-16). Given the risk of nodal involvement, some have suggested that multimodality therapy is highly recommended in the management of clinical T2N0 esophageal cancer (6,10), while other groups recommend upfront surgery (5,7-9,17). The purpose of our study was to determine accuracy of clinical staging of T2N0 esophageal cancer identified from the National Cancer Database (NCDB) in a modern time period [2004–2013].

Methods

Patients

The NCDB is a dataset maintained by the American College of Surgeons and the American Cancer Society and collects patient data from >1,500 centers across the United States. Patients were eligible for analysis if they had clinical T2N0M0 esophageal cancer treated between 2004 and 2013 with upfront esophagectomy.

Statistics

To estimate the accuracy of clinical staging among the cT2N0 patient population, pathologic staging data were used to calculate the respective rates of T and N upstaging and downstaging after resection for the upfront surgery group. Univariate and multivariable Cox proportional hazard models were developed to determine predictors of upstaging. Included in the models were age, sex, tumor location, tumor grade, tumor length, and tumor histology. All statistical tests were two-sided and α (type I) error <0.05 was considered statistically significant. Statistical analysis was performed using SPSS® version 23.0 (IBM®, Chicago, IL, USA). This study was approved as exempt by the Institutional Review Board.

Results

Patient characteristics are presented in *Table 1*. We

Table 2 Accuracy by year of surgery

Year	% correct	% tumor downstage	% tumor upstage	% nodal upstage	% pT0–2N+/pT3–4 (upstage)	% pT0–1N0 (downstage)	% pT0–2N0 (correct/ downstage)
2004	39.3	19.6	21.4	19.6	41.1	19.6	58.9
2005	42.8	15.1	26.1	16.0	42.0	15.1	57.9
2006	34.1	24.6	23.9	17.4	41.3	24.6	58.7
2007	37.5	21.3	20.6	20.6	41.3	21.3	58.8
2008	34.2	21.5	24.2	20.1	44.3	21.5	55.7
2009	35.9	21.8	22.2	20.1	42.3	21.8	57.7
2010	26.2	28.3	29.5	16.0	45.6	28.3	54.5
2011	19.6	31.5	30.6	18.3	48.9	31.5	51.1
2012	20.2	30.9	34.6	14.4	48.9	30.9	51.1
2013	28.5	32.2	22.4	16.8	39.3	32.2	60.7
Overall	30.7	25.5	25.9	17.9	43.8	25.5	56.2

Table 3 Accuracy by tumor length and grade

cT2N0	All	Tumor length			Tumor grade		
		≤3 cm	>3 cm	P	Well/mod	Poor	P
pT2N0	565	308 (54.5)	257 (45.5)	0.66	309 (54.7)	256 (45.3)	0.01
pT0–1N0	469	340 (72.5)	129 (27.5)	<0.001	308 (65.7)	161 (34.3)	<0.001
pT0–2N0	1034	648 (62.7)	386 (37.3)	<0.001	617 (59.7)	417 (40.3)	<0.001
pT3–4N0	175	78 (44.6)	97 (55.4)	0.01	73 (41.7)	102 (58.3)	0.02
pT1–2N+	327	166 (50.8)	161 (49.2)	0.23	141 (43.1)	186 (56.9)	0.004
pT3–4N+	301	95 (31.6)	206 (68.4)	<0.001	95 (31.6)	206 (68.4)	<0.001

identified 1,840 patients with clinical T2N0 esophageal cancer treated from 2004–2013. The median age was 67 years. The median tumor length was 3 cm. The majority of patients were male, had distal tumors, pT2N0 disease, node negative, margin negative, and had adenocarcinomas.

Clinical staging in US patients was accurate pathologically in 30.7% of patients (*Table 2*). Overall accuracy decreased with time. In 2004, accuracy was 39.3% versus 28.5% in 2013. However, rates of pT0–2N0 patients, remained stable. Overall rates of pT0–2N0 staging was 56.2%, 58.9% in 2003, and 60.7% in 2013. Tumor downstaging was seen in 25.9%, tumor upstaging was seen in 25.5%, and nodal upstaging was seen in 17.9%.

Table 3 illustrates the impact of tumor length and grade on accuracy of staging. For patients with accurate pathologic staging or pathologic downstaging, there was a significant association with tumor length ≤3 cm and well to moderately differentiated tumors. In patients with pT0–2N0 staging, 62.7% and 59.7% had tumor length ≤3 cm (P<0.001) and well/moderately differentiated tumors (P<0.001), respectively. In addition, tumor length >3 cm (P<0.001) and poorly differentiated tumors (P<0.001) significantly correlated to tumor and nodal upstaging. *Table 4* shows the impact of esophagectomy facility volume on accuracy of staging. Interestingly, low volume institutions had higher accuracy compared to medium and high-volume centers. Univariate and multivariate analysis of factors prognostic for predicting pT0–2N0 are presented in *Table 5*. Younger age, tumor length >3 cm, and poorly differentiated tumors, and high esophagectomy

Table 4 Accuracy by facility volume

Variable	Low (<10/year)	Medium (10–20/year)	High (>20/year)	P
30-day mortality	48 (5.1)	8 (2.3)	7 (2.1)	0.01
90-day mortality	85 (9.1)	15 (4.2)	16 (4.8)	0.002
pT2N0	366 (33.9)	124 (30.9)	75 (20.9)	<0.001
pT0–2N0	606 (56.1)	246 (61.3)	182 (50.8)	0.01

Table 5 Univariate and multivariate analysis for predicting pT0–2N0

Variable	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age	0.99	0.98–0.99	0.03	0.99	0.98–0.99	0.02
Gender						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.76	0.60–0.96	0.02	0.81	0.63–1.05	0.11
Location						
Middle	Ref	Ref	Ref	Ref	Ref	Ref
Lower	1.42	0.99–2.04	0.06	1.33	0.88–2.00	0.17
GEJ	1.73	1.21–2.47	0.003	1.66	1.10–2.52	0.02
Overlap	1.21	0.59–2.51	0.6	1.16	0.54–2.50	0.7
Tumor length						
≤3 cm	Ref	Ref	Ref	Ref	Ref	Ref
>3 cm	2.29	1.90–2.76	<0.001	2.17	1.78–2.63	<0.001
Grade						
Well/moderate	Ref	Ref	Ref	Ref	Ref	Ref
Poor	2.38	1.97–2.87	<0.001	2.21	1.82–2.69	<0.001
Histology						
Adenocarcinoma	Ref	Ref	Ref	Ref	Ref	Ref
Squamous cell	0.91	0.69–1.20	0.5	1.2	0.85–1.67	0.3
Facility volume						
Low (<10/year)	Ref	Ref	Ref	Ref	Ref	Ref
Medium (10–20/year)	0.8	0.64–1.02	0.07	0.87	0.68–1.12	0.28
High (>20/year)	1.23	0.97–1.57	0.08	1.3	1.01–1.68	0.04

GEJ, gastroesophageal junction.

Table 6 Previous published studies

Study	N	% accuracy	% T-downstage	% T-upstage	% N-upstage
Stiles 2011	40	12.5	30	40	55
Zhang 2012	14	28.6	42.9	21.4	21.4
Crabtree 2013	482	27.4	25.9	18	44.5
Hardacker 2014	35	8.5	42.8	48.5	40
Shin 2014	66	15	60.6	16.7	39
Tekola 2014	38	21	45	17	50
Speicher 2014	786	26.7	30	27.7	30.2
Dolan 2016	16	6	38	56	52
Markar 2016	285	26	35.7	34.8	50
Current study	1,840	30.7	25.5	25.9	17.9

volume were prognostic for upstaging, while gender, tumor location, and tumor histology were not prognostic.

Discussion

This is the largest and most modern report of accuracy clinical T2N0 esophageal cancer from the NCDB. The overall accuracy of clinical staging pathologically was only 30.7% and decreased with time, however, rates of pT0–2N0 were stable (overall 56.2%). Tumor and nodal upstaging were found in 25.9% and 17.9% of patients, respectively, while tumor downstaging was found in 25.5% of patients. Factors related to pathologic upstaging included younger age, tumor length >3 cm, high grade tumors, and high esophagectomy volume centers.

The accuracy of staging for clinical T2N0 esophageal cancer is one of the most important factors when considering treatment recommendations for preoperative therapy. In a NCBD analysis of clinical T2N0 esophageal cancer from 2006–2012, 932 patients underwent upfront esophagectomy (18). Of the 713 patients with complete pathologic data, 326 (45.7%) were upstaged, 26.7% tumor upstaging, 30.1% nodal upstaging, 43.3% with both. Upstaged patients were more likely to have high grade tumors. Age and tumor size was not predictive of upstaging. In an analysis of 482 patients with clinical T2N0 esophageal cancer who underwent esophagectomy, 46.7% were pathologically upstaged. Factors identified as prognostic for upstaging on MVA included male gender, higher Zubrod score, and absence of prior thoracic surgery (12). Grade was not included in the MVA. Age and tumor size were not prognostic. This study is the first to show that younger age and tumor length strongly correlated with pathologic upstaging.

Interestingly, we also found a direct correlation with esophagectomy volume and lower accuracy. NCDB does not provide information on gastroenterology staging volume. We hypothesize that this finding maybe related to more aggressive surgeons in high volume centers and the controversy of neoadjuvant therapy prior to publication on recent randomized trials and meta-analyses (2,3).

Several published studies have shown very poor accuracy for staging clinical T2N0 esophageal cancer (6,9,10,12, 14-17,19) (*Table 6*). Accuracy ranged from 6% to 28.6% as compared to 30.7% in this study. Tumor upstaging ranged from 17% to 40%, compared to 25.9% in this study. Nodal upstaging was notably lower in this study (17.9%) compared 30% to 55% in the other reported studies. This is likely due to the large number of patients included in this analysis. Given the risk of nodal involvement, some have suggested that multimodality therapy is highly recommended in the management of clinical T2N0 esophageal cancer (6,10), while other groups recommend upfront surgery (5,7-9,17). Despite the increased risk of pathologically involved lymph nodes at the time of surgery, no study has reported any OS benefit associated with NCR (5-10,15,17). Speicher *et al.* reported on a NCDB analysis of clinical T2N0 esophageal cancer of patients treated between 1999 and 2011 (9). There was no difference in OS associated with neoadjuvant therapy. More recently, Markar *et al.* reported on long-

term outcomes of 355 clinical T2N0 esophageal patients of which 70 (19.7%) received neoadjuvant therapy (17). Data was collected from 30 European Centers between 2000 and 2010. They reported no difference in survival.

Conclusions

We present the largest and most modern report of accuracy clinical T2N0 esophageal cancer from the NCDB. The overall accuracy of clinical staging pathologically was only 30.7% and decreased with time, however, rates of pT0–2N0 were stable (overall 56.2%). Factors related to pathologic upstaging included younger age, tumor length >3 cm, high grade tumors, and high volume esophagectomy centers.

Acknowledgements

None.

Footnote

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

Ethical Statement: This study was reviewed by the Sarasota Memorial Hospital Institutional Review Board (#16-ONC-03) and determined exempt because it does not meet the definition of human subject research.

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Cite this article as: 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(5):887-893. doi: 10.21037/jgo.2018.01.16

