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Gastrointestinal Cancer

Prognostic Implications of Tumor Differentiation in Clinical T1N0 Gastric Adenocarcinoma

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Key Words. Gastric adenocarcinoma • Clinical T1N0 • Poor differentiation

Abstract

Background. Current guidelines recommend neoadjuvant chemotherapy in patients with locoregional gastric adenocarcinoma. Patients diagnosed with early stage gastric adenocarcinoma are usually managed with upfront surgical intervention. However, pathologic staging in a subset of these clinically staged patients identifies more advanced locoregional disease requiring adjuvant treatment. Therefore, identifying these patients prior to surgical intervention is critical to ensure employment of the appropriate treatment paradigm. The aim of the current study was to define patient characteristics associated with clinical understaging in early gastric cancer.

Methods. Using the National Cancer Database (2004–2014) we identified 3,892 individuals with clinical T1N0 gastric adenocarcinoma who underwent upfront definitive surgery, had negative surgical margins, and did not receive preoperative chemotherapy or radiotherapy. Patient characteristics were compared between those with pathologic stage T1N0 disease and those who were upstaged upon surgery.

Results. Twenty-seven percent of clinical T1N0 gastric adenocarcinomas had a change in stage because of pathologically defined ≥T2 disease or positive lymph nodes. Individuals who were upstaged had a higher tumor grade compared with those with pathologic stage T1N0 disease. Specifically, 41.9% (530/1,264) of individuals with a poorly differentiated tumor were upstaged, compared with only 10.7% (70/656) with a well-differentiated tumor. Approximately 75% of cases involved upstaging because of T misclassification. The highest percentage of upstaging was shown for tumors located at the fundus and body of the stomach.

Conclusion. Upstaging of clinical T1N0 gastric adenocarcinoma is characterized by higher tumor grade and is mostly a result of a change in T stage. These findings mandate thorough workup in order to identify patients with clinically staged T1N0 disease requiring preoperative chemotherapy.

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Implications for Practice: Upstaging of clinical T1N0 gastric adenocarcinoma is characterized by higher tumor grade and is mostly a result of a change in T stage. These findings mandate thorough workup in order to identify patients with clinically staged T1N0 disease requiring preoperative chemotherapy.

Introduction

Patients with clinically staged T1N0 (cT1N0) gastric adenocarcinoma are initially managed with upfront endoscopic resection or surgery. In the absence of a higher pathologic staging following surgery these patients are then offered surveillance, without adjuvant chemotherapy or radiotherapy. According to current National Comprehensive Cancer Center

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Table 1. Patient characteristics

Characteristic	All (*n* = 3,892)	cT1N0pT1N0 (*n* = 2,838)	cT1N0pT2+/Npos (*n* = 1,054)	*p* value
Age, median (IQR)	70 (62–77)	70 (62–77)	70 (62–78)	.50
Sex, male, *n* (%)	2,563 (65.9)	1,859 (65.5)	704 (66.8)	.45
Race, *n* (%)				.09
White	2,884 (74.1)	2,103 (74.1)	781 (74.1)	
Black	524 (13.5)	365 (12.9)	159 (15.1)	
Other	484 (12.4)	370 (13.0)	114 (10.8)	
CDCC, *n* (%)				.51
0	2,429 (62.4)	1,791 (63.1)	638 (60.5)	
1	1,058 (27.2)	755 (26.6)	303 (28.8)	
≥2	405 (10.4)	292 (10.3)	113 (10.7)	
Grade, *n* (%)				<.001
Well differentiated	656 (16.9)	586 (20.7)	70 (6.6)	
Moderately differentiated	1,633 (42.0)	1,216 (42.9)	417 (39.6)	
Poorly differentiated	1,264 (32.5)	734 (25.9)	530 (50.3)	
Undifferentiated	31 (0.8)	17 (0.6)	14 (1.3)	
Other	308 (7.9)	285 (10.0)	23 (2.2)	
CEA,[a] ng/mL				.81
Median (IQR)	1.9 (1.1–3.3)	2.0 (1.2–3.5)	1.7 (1.1–3.1)	
Mean ± SD	3.32 ± 5.35	3.27 ± 5.12	3.42 ± 5.78	

[a]CEA levels were available for 212 out of 2,838 (7.5%) individuals with cT1N0 and pT1N0 disease and for 101 out of 1,054 (9.6%) individuals with cT1N0 and pT2+/Npos disease.

Abbreviations: CDCC, Charlson-Deyo comorbidity condition; CEA, carcinoembryonic antigen; cT1N0, clinically staged T1N0; IQR, interquartile range; pT1N0, pathologically staged T1N0; pT2+/Npos, pathologic staging of at least T2 or positive lymph nodes.

(NCCN) guidelines, patients with clinical staging of T2 or higher or positive lymph nodes (cT2+/Npos) are offered perioperative chemotherapy (category 1 level of evidence), upfront surgery (category 2A), or preoperative chemoradiation (category 2B). Patients with cT1N0 disease who are upstaged upon surgery to pathologic staging of T2+/Npos are offered adjuvant chemotherapy with or without radiotherapy.

Staging of early gastric cancer according to NCCN guidelines includes performing chest-abdomen-pelvic computed tomography (CT) scan and endoscopic ultrasound (EUS). Fluorodeoxyglucose–positron emission tomography (FDG-PET)/CT is recommended in the absence of metastatic disease; however, it may not be appropriate in T1 disease.

Preoperative staging in gastric cancer relies mainly on EUS and chest-abdomen-pelvic CT scan. Using EUS is recommended by NCCN guidelines if early stage disease is suspected or if early versus locally advanced disease needs to be determined. This recommendation is based on the superiority of EUS over CT in assessing T stage [1–4]. In addition, EUS also offers a slightly greater accuracy over CT in evaluating N stage [3, 5–10]. However, less than 25% of patients with gastric cancer undergo preoperative EUS staging [11]. The diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and from 30% to 90% for N staging [11, 12].

The current study evaluated the frequency of upstaging following surgery among patients with cT1N0 gastric cancer and aimed to define corresponding patient characteristics, allowing better identification of those requiring preoperative chemotherapy. The overarching goal was to guide clinicians on the optimal staging modality in order to allow better adherence to category 1 level of evidence in gastric cancer.

Materials and Methods

Data Source and Patient Population

Our cohort was derived from the National Cancer Database (NCDB), a hospital-based cancer registry, from 2004 to 2014. The NCDB captures data on 70% of cancer diagnoses in the U.S. from more than 1,400 hospitals with cancer programs accredited by the American College of Surgeons' Commission on Cancer and the American Cancer Society [13]. All individuals with clinical T1N0 gastric adenocarcinoma who underwent definitive surgery, had negative surgical margins, and did not receive preoperative chemotherapy or radiotherapy were included in the analysis.

Definition of Variables

Covariates included age, sex, race, patient comorbidities (Charlson-Deyo comorbidity condition) [14, 15], tumor grade, and preoperative carcinoembryonic antigen (CEA) levels. Race and ethnicity were used to create a composite variable categorized as White, Black, or other/unknown. Tumor grade was defined as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. Tumor location within the stomach was defined as found at

Table 2. Misclassification according to primary tumor location within the stomach

Primary site	Number of cases (*n* = 3,892) (%)	T2+/Npos*n* (% per location)
Cardia	1,546 (39.7)	363 (23.5)
Fundus	132 (3.4)	43 (32.6)
Body	303 (7.8)	106 (35.0)
Pyloric antrum	905 (23.3)	244 (27.0)
Pylorus	63 (1.6)	15 (23.8)
Lesser curvature	331 (8.5)	106 (32.0)
Greater curvature	153 (3.9)	53 (34.6)
Overlapping sites	136 (3.5)	54 (39.7)
Unspecified	323 (8.3)	70 (21.7)

Abbreviation: T2+/Npos, stage T2 or higher or positive lymph nodes.

the cardia, fundus, body, pyloric antrum, pylorus, lesser curvature, greater curvature, overlapping sites, or unspecified.

Statistical Analysis

Patients characteristics were compared using Student's *t* test for continuous variables and chi-squared test for dichotomous variables.

All statistical analyses were performed using Stata/IC software 13.0 (StataCorp, College Station, TX). A two-sided *p* value of <.05 was used to define significance.

Results

We identified 3,892 individuals with clinical T1N0 gastric adenocarcinoma who underwent definitive surgery, had negative surgical margins, and did not receive neoadjuvant chemotherapy or radiotherapy. The median follow-up time was 38.7 months (interquartile range, 20.5–61.3). Of those individuals, 1,054 individuals (27.1%) were misclassified and had postoperative pathologic staging of at least T2 or positive lymph nodes (pT2+/Npos). Patient characteristics are presented in Table 1. Individuals with cT1N0 and subsequent pT2+/Npos tumors were significantly more likely to have a higher tumor grade compared with individuals with cT1N0 and pathologically staged T1N0 (pT1N0) tumors ($p < .001$, Table 1). Specifically, 41.9% (530 out of 1,264) of individuals with a poorly differentiated tumor were found to have a higher pathologic stage, compared with only 25.5% (417 out of 1,633) with a moderately differentiated tumor and 10.7% (70 out of 656) with a well-differentiated tumor. The percentage of individuals found to have a higher pathologic stage was associated with primary site location within the stomach, with a greater percentage at the fundus and body, compared with a lower percentage at the cardia and pylorus ($p < .001$, Table 2). The percentage of individuals with a higher pathologic stage was not associated with year of diagnosis (data not shown). There was no difference between individuals with cT1N0 and subsequent pT1N0 disease or those with subsequent pT2+/Npos disease in terms of the number of days from diagnosis to surgery (median 34 days for both).

Table 3. Misclassification according to T and N staging

pNpT	0	1	2	3	3A	3B	X	Total
1	0	86	7	1	0	0	0	**94**
1A	0	18	8	0	1	0	0	**27**
1B	0	123	34	3	1	0	0	**161**
2	170	54	26	7	5	0	1	263
2A	46	19	3	0	0	0	0	68
2B	39	35	11	0	0	0	0	85
3	98	98	49	10	15	2	2	274
4	3	6	2	0	0	0	0	11
4A	18	11	13	2	11	0	1	56
4B	2	5	1	1	1	0	0	10
X	0	1	2	0	0	0	0	3
Total	**376**	456	156	24	34	2	4	**1,052**

We next assessed the weight of a change in pathologic stage for either T or N categories. Out of the 1,054 individuals who were upstaged, 35.7% ($n = 376$) were upstaged because of a change in T stage, 26.7% ($n = 282$) because of a change in N stage, and 37.6% ($n = 396$) because of a change in both T and N stages. Hence, approximately 75% of cases involved upstaging because of a change in T stage, and approximately 64% of cases involved upstaging because of a change in N stage. The details of this analysis are shown in Table 3. There was not a statistically significant association between primary tumor location within the stomach and the weight of T or N upstaging (data not shown).

Discussion

In the current study, we demonstrate that almost 30% of clinical T1N0 gastric adenocarcinomas had pathologic staging of at least T2 or positive lymph nodes. Approximately 75% and 64% of cases involved a change in T and N stage, respectively. Upstaging was associated with poor differentiation of the tumor and with tumor location at fundus and body of the stomach. To the best of our knowledge, this is the first study to estimate the extent of upstaging among clinical stage T1N0 gastric adenocarcinoma.

The higher percentage of upstaged tumors located at the fundus and body, compared with the lower percentage of tumors located at the cardia and pylorus, may be explained by both the width of the anatomical structures and the presence or absence of gastric folds. The narrow nature of the cardia and pylorus allows better circumferential apposition of the gastric wall to the EUS transducer with subsequent better reading, compared with the wider nature of the fundus and body of stomach. Gastric folds, which are present in the fundus and body of the stomach and absent in the cardia and pylorus, may interfere with accurate reading of the depth of tumor invasion.

Our results suggest including EUS as part of the preoperative workup in gastric cancer, mainly in those with poorly

differentiated tumors. For tumors located at the fundus and body of the stomach, the endoscopist should pay special attention to gastric folds and make every effort to minimize the distance between the transducer and the gastric wall.

This study had several limitations. First, the NCDB lacks information on the modalities used for staging, that is, EUS, CT scan, and/or FDG-PET/CT. Therefore, we could not test the correlation between the specific modality used and the frequency of upstaging. Second, CEA levels were available for only 8% of the study population and therefore could not be accurately assessed as a possible prognostic or predictive marker.

The main strength of this study was using the NCDB, a large cohort of a hospital-based cancer registry, capturing data on 70% of cancer diagnoses in the U.S. This database enabled the precise definition of both clinical and pathologic staging of gastric adenocarcinoma. In addition, the NCDB contains data on chemotherapy, radiotherapy administration, and surgical margins status, allowing an accurate definition of true T1N0 disease.

Conclusion

Upstaging of clinical T1N0 gastric adenocarcinoma is found in approximately 30% of patients and is characterized by higher tumor grade and is mostly a result of a change in T stage. These findings suggest using EUS as part of preoperative workup in patients with clinical T1N0 disease, allowing better identification of those requiring preoperative chemotherapy.

Author Contributions

Conception/design: Ofer Margalit, Einat Shacham-Shmueli, Ben Boursi
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Disclosures

Talia Golan: AstraZeneca, Merck/Merck Sharp & Dohme (RF), AstraZeneca, Abbvie, Teva, Bayer, Merck/Merck Sharp & Dohme (C/A), Abbvie, Bioline, Roche (H); **Ronac Mamtani:** Roche, Seattle Genetics/Astellas, Flatiron Health (C/A). The other authors indicated no financial relationships.

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