Prognostic Implications of Tumor Differentiation in Clinical T1N0 Gastric Adenocarcinoma

Ofer Margalit,† Einat Shacham-Shmueli,† Yu-Xiao Yang, Yaacov R. Lawerence, Idan Levy, Kim A. Reiss, Talia Golani, Naama Halpern, Dan Aderka, Bruce Giantonio, Ronac Mamtani, Ben Boursi
Departments of Oncology and Gastroenterology, Sheba Medical Center, Tel-Hashomer, Israel; Tel-Aviv University, Tel-Aviv, Israel; Center for Clinical Epidemiology and Biostatistics and Division of Gastroenterology, Department of Medicine, Perelman School of Medicine, and Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA; Department of Radiation Oncology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, USA; Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
†Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

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.

The Oncologist 2021;26:e111–e114

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...
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 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, 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               |         |

*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.
The difference between individuals with cT1N0 and subsequent individuals with a higher pathologic stage was not associated with poor differentiation of the tumor and with tumor location at fundus and body of 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 cardia and pylorus. 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 differentiable tumors located at the cardia and pylorus, compared with the wider nature of the cardia and pylorus. This may explain why the higher percentage of upstaged tumors located at the cardia and pylorus, compared with the higher 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.

The Oncologist published by Wiley Periodicals LLC on behalf of AlphaMed Press.
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.

## References

1. Harris KM, Kelly S, Berry E et al. Systematic review of endoscopic ultrasound in gastro-oesophageal cancer. Health Technol Assess 1998; 2:i–iv, 1–134.
2. Meining A, Dittler HJ, Wolf A et al. You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. Gut 2002;50:599–603.
3. Willis S, Truong S, Gribnitz S et al. Endoscopic ultrasonography in the preoperative staging of gastric cancer: Accuracy and impact on surgical therapy. Surg Endosc 2000;14:951–954.
4. Yeung HW, Macapinlac H, Karpeh M et al. Accuracy of FDG-PET in gastric cancer. Preliminary experience. Clin Positron Imaging 1998;1:213–221.
5. Botet JF, Lightdale CJ, Zauber AG et al. Preoperative staging of gastric cancer: Comparison of endoscopic US and dynamic CT. Radiology 1991; 181:426–432.
6. de Manzoni G, Pedrazzani C, Di Leo A et al. Experience of endoscopic ultrasound in staging adenocarcinoma of the cardia. Eur J Surg Oncol 1999;25:595–598.
7. Fukuya T, Honda H, Hayashi T et al. Lymph-node metastases: Efficacy for detection with helical CT in patients with gastric cancer. Radiology 1995;197:705–711.
8. Kelly S, Harris KM, Berry E et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. Gut 2001;49:534–539.
9. Pollack BJ, Chak A, Sivak MV Jr. Endoscopic ultrasonography. Semin Oncol 1996;23:336–346.
10. Tsiodras T, Jun SM, Mian XH. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. World J Gastroenterol 2006;12:43–47.
11. Spolverato G, Ejaz A, Kim Y et al. Use of endoscopic ultrasound in the preoperative staging of gastric cancer: A multi-institutional study of the US gastric cancer collaborative. J Am Coll Surg 2015;220:48–56.
12. Cardoso R, Coburn N, Seevaratnam R et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer 2012;15(suppl 1):519–526.
13. Winchester DP, Stewart AK, Bura C et al. The National Cancer Data Base: A clinical surveillance and quality improvement tool. J Surg Oncol 2004;85:1–3.
14. Charlson ME, Pompei P, Ales XL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
15. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45:613–619.