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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Adjuvant Therapy is Associated with Improved Survival in pT1N1 Gastric Cancer in a Heterogeneous Western Patient Population

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ABSTRACT

Background. Two recent South Korean studies showed adjuvant therapy (AT) was not associated with improved survival in pT1N1 gastric adenocarcinoma (GAC). We established the prognostic utility of lymph node status, determined the pattern of use of AT, and compared survival stratified by type of AT in pT1N1 GAC in a Western patient population.

Methods. We identified patients with pT1N0 and pT1N1 GAC using the National Cancer Database from 2004 to 2012. Clinicopathologic variables, treatment regimens, and overall survival (OS) were compared.

Results. We compared 4516 (86.6%) pT1N0 to 696 (13.4%) pT1N1 patients. pT1N1 tumors were larger (median size 2.5 vs. 1.8 cm, $p < 0.001$), more often poorly differentiated (56.2% vs. 39.6%, $p < 0.001$), and had higher median retrieved lymph nodes (RLN) (14 vs. 12, $p < 0.001$) compared with pT1N0. pT1N1 was associated with worse median overall survival (OS) (6.9 vs. 9.9 years for pT1N0, $p < 0.001$). pN1 was independently associated with worse OS (hazard ratio [HR] 2.17, 95% confidence interval [CI] 1.84–2.56). Increased RLN was associated with improved OS (HR 0.73, 95% CI 0.65–0.83). Among pT1N1 patients, 330 (47.4%) had observation (OBS), 77 (11.1%) received adjuvant chemotherapy (ACT), 68 (9.8%) received adjuvant radiation therapy (ART), and 221 (31.8%) received adjuvant chemoradiation therapy (ACRT). ACT and ACRT were independently associated with improved OS (HR 0.37, 95% CI 0.22–0.65 and HR 0.40, 95% CI 0.28–0.57).

Conclusions. pN1 was associated with worse survival and RLN $\geq$ 15 was associated with improved survival in pT1 GAC. ACT and ACRT were independently associated with improved survival in pT1N1 gastric cancer suggesting a valuable role in Western patients.

Adjuvant therapy reduces the risk of systemic recurrence and prolongs survival for gastric adenocarcinoma patients as demonstrated by previously published, randomized, clinical trials.[1,2] However, the use of adjuvant therapy is most beneficial in patients with the highest risk of distant recurrence and should be balanced against its toxicities. The presence of any degree of regional lymph node disease is a known risk factor for recurrence, and the National Comprehensive Cancer Network (NCCN) recommends adjuvant therapy for patients with any number of positive lymph nodes.[3]

Two recent retrospective studies from South Korea showed that patients with pT1N1 (1 or 2 lymph nodes involvement) gastric cancer might not benefit from adjuvant therapy.[4,5] The studies demonstrated that surgery with adjuvant therapy (chemotherapy or chemoradiotherapy) was not associated with any benefit in progression-free survival or disease-free survival in patients with pT1N1 disease.[4,5] These findings further imply that patients with T1 tumors with metastasis to one or two lymph nodes have the same prognosis as patients with no lymph node involvement. Their results strengthen the recommendations of the Japanese Gastric Cancer Treatment Guidelines, which advocate observation without adjuvant treatment

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TABLE 1 Comparison of the clinicopathological features of pT1N0 and pT1N1 gastric adenocarcinoma

	pT1N0 $n = 4509$	pT1N1 $n = 696$	p
Age, median yr (SD)	69.0 (12.0)	69.0 (12.6)	0.063
Gender, *n* (%)			
Male	2745 (60.9)	433 (62.2)	0.502
Female	1764 (39.1)	263 (37.8)	
Race/ethnicity, *n* (%)			
Non-Hispanic white	2986 (66.2)	446 (64.1)	0.599
Non-Hispanic black	592 (13.1)	91 (13.1)	
Hispanic	377 (8.4)	66 (9.5)	
Asian	554 (12.3)	93 (13.1)	
Insurance status, *n* (%)			
Not insured	73 (1.6)	11 (1.6)	0.467
Private	1510 (33.5)	243 (34.9)	
Medicaid/medicare	2854 (63.3)	426 (61.2)	
Unknown	72 (1.6)	16 (2.3)	
Hospital type, *n* (%)			
Community	2312 (51.3)	365 (52.4)	0.566
Academic	2197 (48.7)	331 (47.6)	
Charlson–Deyo score, *n* (%)			
< 2	4081 (90.5)	627 (90.1)	0.725
≥ 2	428 (9.5)	69 (9.9)	
Resection, *n* (%)			
Subtotal gastrectomy	3451 (76.5)	517 (74.3)	0.193
Total gastrectomy	1058 (23.5)	179 (25.7)	
Tumor location, *n* (%)			
Cardia	1536 (34.1)	257 (36.9)	0.009
Fundus/body	561 (12.4)	71 (10.2)	
Pylorus/antrum	1538 (34.1)	209 (30.0)	
Lesser curve/greater curve	694 (15.4)	117 (16.8)	
Overlapping	180 (4.0)	42 (6.0)	
Tumor size, median cm (SD)	1.8 (1.7)	2.5 (3.3)	< 0.001
Histological type, *n* (%)			
Adenocarcinoma, unspecified	2858 (63.4)	444 (63.8)	0.866
Signet	793 (17.6)	114 (16.4)	
Diffuse	134 (3.0)	22 (3.2)	
Intestinal	724 (16.1)	116 (16.7)	
Grade, *n* (%)			
Well/moderately differentiated	2414 (53.5)	282 (40.5)	< 0.001
Poorly/anaplastic differentiated	1787 (39.6)	391 (56.2)	
Unknown	308 (6.8)	23 (3.3)	
Lymphovascular invasion, *n* (%)			
* % of patients with known LVI status	165/1529 (10.8)	118/241 (49.0)	<
0.001			
Number of retrieved LNs, median (SD)	12 (9.9)	14 (10.6)	<
0.001			
Treatment, *n* (%)			
Surgery alone	4424 (98.1)	330 (47.4)	<
0.001			
Surgery + adjuvant chemotherapy	41 (0.9)	77 (11.1)	
Surgery + adjuvant radiation	17 (0.4)	68 (9.8)	
Surgery + adjuvant chemoradiation	27 (0.6)	221 (31.8)	
Readmitted within 30 days, *n* (%)			
No	4091 (90.7)	643 (92.4)	0.157
Yes	418 (9.3)	53 (7.6)	

after curative resection for pT1N1 patients, and challenge the recommendations published by the NCCN.[6,7] However, given the overwhelming evidence demonstrating marked disparities in gastric cancer outcomes between Eastern and Western patients, caution should be exercised before extrapolating the results of these studies to a Western patient population without clearer evidence regarding the role of adjuvant therapy in pT1N1 gastric cancer in such a group.[8–10]

The purpose of this study was to establish the prognostic utility of lymph node status in early gastric cancers in a Western population using the National Cancer Database. Additionally, this study determined the utilization pattern of adjuvant therapy in pT1N1 gastric cancer in the United States and determined whether there is an associated survival benefit with adjuvant therapy.

MATERIALS AND METHODS

Following approval from the UT Southwestern Medical Center Institutional Review Board, we queried the National Cancer Database (NCDB) participant user file (PUF) for patients with gastric cancer (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3], topographical code C16.0) diagnosed between 2004 and 2012. The NCDB is a national cancer registry that receives information from more than 1500 Commission-on-Cancer-

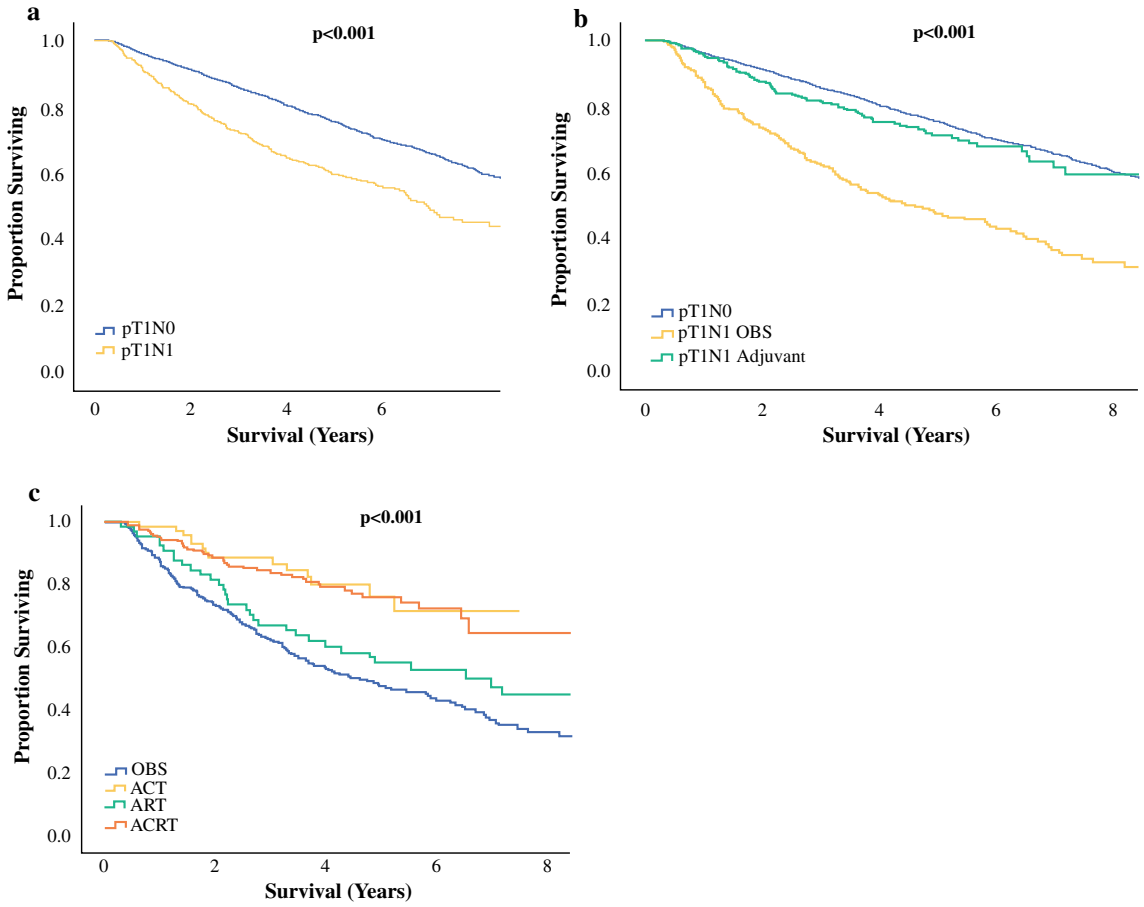

FIG. 1 Overall survival for **a** pT1N0 and pT1N1 gastric adenocarcinoma, **b** pT1N0, pT1N1 OBS, and pT1N1 adjuvant gastric adenocarcinoma, **c** pT1N1 gastric adenocarcinoma stratified by specific adjuvant therapy regimen

accredited cancer programs in the United States and captures approximately 70% of incident cases in the United States.[11]

We identified all patients older than age 18 years, with the histologic diagnosis of adenocarcinoma of the stomach as defined by ICD-O-3 morphological codes 8140, 8142, 8143, 8144, 8145, 8255 and 8490. Neuroendocrine cancers, sarcomas, and squamous cancers were excluded from the study. Serial exclusion of non pT1 tumors, non pN0 or pN1 nodal status, metastatic disease, patients who did not undergo surgical resection or had unknown surgical resection, patients with nonradical operations, patients with R1 or R2 surgical margins, patients who received neoadjuvant chemotherapy, patients who died within 90 days of surgery, and unknown vital status was performed. pN1 was defined by the 7th edition of the American Joint Committee on Cancer (AJCC) criteria. The 6th edition defined one to six positive lymph nodes as pN1, whereas the 7th edition defined one to two positive lymph nodes as pN1. We therefore excluded patients who had unknown number of positive lymph nodes documented as pN1 or who had 3–6 positive lymph nodes documented as pN1 in the prior staging edition.

We abstracted data from the NCDB PUF on patient age, gender, race/ethnicity, Charlson/Deyo comorbidity score, insurance type, and tumor characteristics, including location, histology, grade, tumor extension, and lymph node status. We used pathological stage according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual. We also abstracted data on location of tumor, type of surgery, tumor size, number of lymph nodes retrieved, number of lymph nodes positive, and receipt of adjuvant chemotherapy and/or radiation therapy. Overall survival was the primary outcome.

We also performed analysis on the incidence of clinical to pathologic upstaging/downstaging. According to NCCN guidelines, neoadjuvant chemotherapy is recommended to patients with cN1 disease; however, we demonstrated the incidence of encountering patients who have pathologic nodal disease but are chemotherapy-naïve because of

TABLE 2 Multivariable cox regression of clinicopathologic variables associated with survival in resected pT1N0 and pT1N1 gastric adenocarcinoma

	Hazard ratio	95% Confidence interval	*p*
Age (year)			
< 50	Reference		
50–65	1.343	0.98–1.84	0.066
≥ 65	2.473	1.84–3.33	< 0.001
Gender			
Male	Reference		
Female	0.820	0.73–0.92	0.001
Race/ethnicity			
Non-Hispanic white	Reference		
Non-Hispanic black	1.059	0.90–1.25	0.496
Hispanic	0.953	0.77–1.18	0.661
Asian	0.667	0.54–0.82	< 0.001
Hospital type			
Community	Reference		
Academic	0.824	0.74–0.92	0.001
Charlson–Deyo score			
< 2	Reference		
≥ 2	1.626	1.39–1.90	< 0.001
Resection			
Subtotal gastrectomy	Reference		
Total gastrectomy	1.199	1.06–1.36	0.005
Tumor size (cm)			
< 2	Reference		
≥ 2	1.392	1.24–1.57	< 0.001
Grade			
Well/moderately differentiated	Reference		
Poorly/anaplastic differentiated	0.973	0.87–1.09	0.633
LV invasion	1.683	1.23–2.30	0.001
Nodal status			
N0	Reference		
N1	2.171	1.84–2.56	< 0.001
No. of retrieved nodes			
< 15	Reference		
≥ 15	0.732	0.65–0.83	< 0.001
Treatment			
Surgery alone	Reference		
Surgery + adjuvant chemotherapy	0.460	0.29–0.73	0.001
Surgery + adjuvant radiation	0.811	0.58–1.14	0.226
Surgery + adjuvant chemoradiation	0.509	0.37–0.70	< 0.001

limitations in adequate staging.[6] Thus, we wanted to identify pT1N1 patients who were not treated with neoadjuvant therapy due to inadequate staging versus those who were clinically staged appropriately but not given neoadjuvant therapy.

Statistical Analysis

Chi square tests and analysis of variance (ANOVA) were used to calculate differences between cohorts. Kaplan–Meier with log-rank univariate analysis was performed for survival analysis. All variables significant in the univariate analysis were placed in the multivariable model. Hazard ratios and confidence intervals for the multivariable model were calculated using Cox proportional hazard regression. All tests were two-sided and performed at the 5% significance level. Statistical analysis was performed using the SPSS statistical software package (Version 22.0 for Macintosh, SPSS Inc, Chicago, IL).

RESULTS

Clinicopathologic Features of Patients with pT1N0 and pT1N1 Gastric Adenocarcinoma

From 2004 to 2012, we identified 5205 cases of resected pT1 gastric adenocarcinoma (pT1N0: 4509, 86.6%; pT1N1: 696, 3.4%) (Supplementary Fig. 1), Table 1 describes the differences in clinicopathologic features between patients with pT1N0 and pT1N1 gastric adenocarcinoma. There was no significant difference in age, gender, race/ethnicity, insurance status, hospital type, Charlson–Deyo score, type of resection, or tumor histology. There were significantly more distal tumors among pT1N0 compared with pT1N1 patients. pT1N1 gastric cancers had significantly larger tumors, a higher rate of poor/anaplastic differentiation, and a higher median number of retrieved lymph nodes compared to pT1N0. Among patients with known lymphovascular invasion status, pT1N1 tumors had higher rates of lymphovascular invasion. Patients with pT1N0 gastric adenocarcinoma were more likely to undergo observation (OBS) (98.1% vs. 47.4%, $p < 0.001$) compared with pT1N1, whereas pT1N1 tumors were treated more often with adjuvant therapy including chemotherapy (ACT: 11.1% vs. 0.9%), radiation therapy (ART: 9.8% vs. 0.4%), and chemoradiotherapy (ACRT: 31.8% vs. 0.6%; $p < 0.001$).

TABLE 3 Comparison of clinicopathologic features of pT1N1 gastric adenocarcinoma stratified by adjuvant therapy type

	OBS $n = 330$	ACT $n = 77$	ART $n = 68$	ACRT $n = 221$	p
Age, median year (SD)	75.0 (11.9)	64.0 (10.3)	67.5 (11.7)	64.0 (11.9)	< 0.001
Gender, *n* (%)					
Male	206 (62.4)	50 (64.9)	45 (66.2)	132 (59.7)	0.733
Female	124 (37.6)	27 (35.1)	23 (33.8)	89 (40.3)	
Race/ethnicity, *n* (%)					
Non-Hispanic white	234 (70.9)	52 (67.5)	46 (67.6)	114 (51.6)	0.001
Non-Hispanic black	33 (10.0)	7 (9.1)	5 (7.4)	46 (20.8)	
Hispanic	26 (7.9)	7 (9.1)	5 (7.4)	28 (12.7)	
Asian	37 (11.2)	11 (14.3)	12 (17.6)	33 (14.9)	
Insurance status, *n* (%)					
Not insured	5 (1.5)	0	2 (2.9)	4 (1.8)	< 0.001
Private	79 (23.9)	37 (48.1)	27 (39.7)	100 (45.2)	
Medicaid/medicare	239 (72.4)	37 (48.1)	37 (54.4)	113 (51.1)	
Unknown	7 (2.1)	3 (3.9)	2 (2.9)	4 (1.8)	
Hospital treated, *n* (%)					
Community	161 (48.8)	33 (42.9)	49 (72.1)	122 (55.2)	0.001
Academic	169 (51.2)	44 (57.1)	19 (27.9)	99 (44.8)	
Charlson–Deyo score, *n* (%)					
< 2	294 (89.1)	68 (88.3)	66 (97.1)	199 (90.0)	0.227
≥ 2	36 (10.9)	9 (11.7)	2 (2.9)	22 (10.0)	
Approach, *n* (%)					
Open	81 (24.5)	25 (32.5)	3 (4.4)	71 (32.1)	< 0.001
Minimally invasive	22 (6.7)	8 (10.4)	1 (1.5)	29 (13.1)	
Unknown	227 (68.8)	44 (57.1)	64 (94.1)	121 (54.8)	
Resection, *n* (%)					
Subtotal gastrectomy	235 (71.2)	57 (74.0)	52 (76.5)	173 (78.3)	0.302
Total gastrectomy	95 (28.8)	20 (26.0)	16 (23.5)	48 (21.7)	
Tumor location, *n* (%)					
Cardia	136 (41.2)	35 (45.5)	26 (38.2)	60 (27.1)	0.069
Fundus/body	35 (10.6)	7 (9.1)	5 (7.4)	24 (10.9)	
Pylorus/antrum	90 (27.3)	17 (22.1)	22 (32.4)	80 (36.2)	
Lesser curve/greater curve	46 (13.9)	15 (19.5)	11 (16.2)	45 (20.4)	
Overlapping	23 (7.0)	3 (3.9)	4 (5.9)	12 (5.4)	
Tumor size, median cm (SD)	2.5 (4.5)	2.5 (2.0)	2.5 (1.5)	2.3 (1.8)	0.561
Histological type, *n* (%)					
Adenocarcinoma, unspecified	220 (66.7)	52 (67.5)	49 (72.1)	123 (55.7)	0.010
Signet	41 (12.4)	9 (11.7)	12 (17.6)	52 (23.5)	
Diffuse	7 (2.1)	3 (3.9)	2 (2.9)	10 (4.5)	
Intestinal	62 (18.8)	13 (16.9)	5 (7.4)	36 (16.3)	
Grade, *n* (%)					
Well/moderately differentiated	149 (45.2)	30 (39.0)	20 (29.4)	83 (37.6)	0.275
Poorly/anaplastic differentiated	171 (51.8)	45 (58.4)	45 (66.2)	130 (58.8)	
Unknown	10 (3.0)	2 (2.6)	3 (4.4)	8 (3.6)	
Lymphovascular invasion, *n* (%)					
* % with known LVI status	44/95 (46.3)	17/35 (48.6)	1/4 (25.0)	56/107 (52.3)	< 0.001
No of retrieved LNs, median (SD)	14.0 (10.9)	13.0 (10.0)	10.0 (6.3)	15.0 (10.9)	< 0.001

TABLE 3 continued

	OBS $n = 330$	ACT $n = 77$	ART $n = 68$	ACRT $n = 221$	p
No. of positive nodes, *n* (%)					
1	243 (73.6)	51 (66.2)	43 (63.2)	139 (62.9)	0.040
2	87 (26.4)	26 (33.8)	25 (36.8)	82 (37.1)	
Readmitted within 30 days, *n* (%)					
No	299 (90.6)	72 (93.5)	64 (94.1)	208 (94.1)	0.414
Yes	31 (9.4)	5 (6.5)	4 (5.9)	13 (5.9)	

Clinical Outcomes and Predictors of Survival in pT1N0 and pT1N1 Gastric Adenocarcinoma

pT1N0 tumors were associated with improved median overall survival of 9.9 years compared with pT1N1 (6.9 years) (Fig. 1a, $p < 0.001$). The 1-, 3-, and 5-year survival rates were 96.2%, 85.9% and 75.6% for pT1N0 and 91.4%, 72.7% and 59.7% for pT1N1. The median follow-up time for pT1N0 patients was 3.7 years and was 3.3 years for pT1N1. Receipt of adjuvant therapy was associated with a survival advantage for node positive patients compared with observation and reflects a survival curve closer to that of pT1N0 patients (Fig. 1b). Median overall survival for pT1N1 patients treated with adjuvant therapy was 9.1 years, significantly greater than observed pT1N1 patients (4.6 years, $p < 0.001$).

In multivariable analysis of the clinicopathological variables associated with overall survival (Table 2), pN1 nodal status was independently associated with significantly worse survival (HR 2.17, 95% CI 1.84–2.56). Other factors associated with worse survival in the multivariable model were age $\geq$ 65 years, Charlson-Deyo score $\geq$ 2, having undergone total gastrectomy, tumor size $\geq$ 2 cm, and presence of lymphovascular invasion.

Although receipt of adjuvant systemic chemotherapy and chemoradiotherapy were most strongly associated with improved survival (ACT: HR 0.46, 95% CI 0.29–0.73; ACRT: HR 0.51, 95% CI 0.37–0.70), adjuvant radiotherapy alone demonstrated no advantage (HR 0.81, 95% CI 0.58–1.14). Beyond receipt of therapy, Asian race was strongly associated with improved survival. Lesser factors associated with improved survival include female gender, care received at an academic center, and an increased number of retrieved nodes.

Clinical Outcomes and Predictors of Survival in pT1N0 and pT1N1 Gastric Adenocarcinoma with $\geq$ 15 RLN

In an effort to avoid the effect of understaging on survival outcomes, we performed a subset analysis of patients who received adequate lymphadenectomy, defined by the NCCN as $\geq$ 15 RLN.[6] This subset analysis did not change the survival difference noted between pT1N0 and pT1N1 cohorts but did demonstrate an associated improvement in overall survival (OS) among both cohorts (median OS was not reached for pT1N0 and 8.2 years for pT1N1, $p < 0.001$). The 1-, 3-, and 5-year survival rates were 97.8%, 89.1% and 80.9% for pT1N0 and 93.1%, 78.7% and 65.1% for pT1N1. pT1N1 treated with adjuvant therapy had similar survival to pT1N0 patients (median OS not reached in both groups) and an associated improvement in survival compared with observation in T1N1 patients (median OS 5.9 years). All types of adjuvant therapy were associated with improved OS compared with OBS in pT1N1 patients. In a multivariable analysis of the factors associated with overall survival in pT1 patients with $\geq$ 15 RLN, pN1 was independently associated with worse OS compared with pN0 disease (HR 2.77, 95% CI 2.11–3.65), and the receipt of adjuvant chemotherapy was independently associated with improved OS (HR 0.26, 95% CI 0.10–0.73 for ACT and HR 0.35, 95% CI 0.21–0.60 for ACRT).

Clinicopathologic Features of Patients with pT1N1 Gastric Adenocarcinoma

Table 3 describes differences in clinicopathologic features of patients with resected pT1N1 gastric adenocarcinoma stratified by type of adjuvant therapy. There was no significant difference in gender, Charlson–Deyo score, type of resection, tumor location, tumor size, tumor grade, or 30-day readmission rates. Patients treated with observation were significantly older, a higher proportion were Non-Hispanic white, and insured by Medicaid/Medicare compared with patients treated with ACT, ART, and ACRT. Patients who received adjuvant radiation therapy were more likely to be treated at community hospitals compared with other cohorts. Patients who received any adjuvant therapy were more likely to have two positive nodes compared with one positive node.

Forty-seven percent of patients with pT1N1 positive cancers underwent observation. A logistic regression was

TABLE 4 Multivariable cox regression of clinicopathologic variables associated with survival in pT1N1 gastric adenocarcinoma

	Hazard ratio	95% Confidence interval	*p*
Age (year)			
< 50	Reference		
50–65	0.917	0.52–1.61	0.763
≥ 65	1.433	0.85–2.43	0.182
Race/ethnicity			
Non-Hispanic white	Reference		
Non-Hispanic black	1.617	1.11–2.36	0.012
Hispanic white	0.946	0.58–1.54	0.825
Asian	0.887	0.59–1.33	0.557
Charlson–Deyo score			
< 2	Reference		
≥ 2	1.321	0.90–1.94	0.154
Resection			
Subtotal gastrectomy	Reference		
Total gastrectomy	1.493	1.13–1.97	0.004
Tumor size (cm)			
< 2	Reference		
≥ 2	1.551	1.16–2.08	0.003
Grade			
Well/moderately differentiated	Reference		
Poorly/anaplastic differentiated	0.856	0.66–1.10	0.231
LV invasion	2.009	1.13–3.56	0.017
No. of positive nodes			
1	Reference		
2	1.266	0.97–1.65	0.085
Treatment			
Surgery alone	Reference		
Surgery + adjuvant chemotherapy	0.373	0.22–0.65	< 0.001
Surgery + adjuvant radiation	0.894	0.62–1.30	0.562
Surgery + adjuvant chemoradiation	0.402	0.28–0.57	< 0.001

performed to determine clinicopathologic factors associated with receipt of adjuvant therapy in pT1N1 gastric cancers. Distal tumor location (odds ratio [OR] 1.64, 95% CI 1.03–2.63 for pylorus/antrum compared with cardia) and two positive nodes (OR 1.47, 95% CI 1.03–2.12 compared with 1 positive node) were independently associated with increased odds of receipt of adjuvant therapy. Older age was independently associated with decreased odds of adjuvant therapy receipt (OR 0.93, 95% CI 0.91–0.94).

Clinical Outcomes and Predictors of Survival in pT1N1 Gastric Adenocarcinoma

Figure 1c represents the overall survival of resected pT1N1 patients stratified by type of adjuvant therapy. The median overall survival was not reached for ACT and ACRT, 7.0 years for ART, and 4.6 years for OBS ($p < 0.001$). The 1-, 3-, and 5-year survival rates were 98.7%, 88.6% and 76.2% for ACT, 94.9%, 84.7% and 76.1% for ACRT, 92.5%, 67.2% and 52.8% for ART, and 86.7%, 62.7% and 47.7% for OBS. The median follow-up time was 2.8 years for OBS, 3.7 years for ACT, 3.4 years for ART, and 3.6 years for ACRT. Table 4 shows a multivariable analysis of clinicopathologic variables associated with survival. The receipt of any adjuvant chemotherapy was independently associated with improved survival after adjusting for other clinicopathological factors (HR 0.37, 95% CI 0.22–0.65 for ACT and HR 0.40, 95% CI 0.28–0.57 for ACRT), but ART was not independently associated with survival. Factors associated with worse survival included undergoing total gastrectomy, tumor size ≥ 2 cm, lymphovascular invasion, and Non-Hispanic black race/ethnicity. The number of positive lymph nodes, one or two, was not significantly associated with survival.

Relationship of Clinical Node Status and Pathologic Node Status

When considering the 5029 patients with cN0 or cNx disease who underwent upfront surgery, 587 (11.7%) were upstaged to pN1 disease at resection. Of the 176 patients with cN1 disease who underwent upfront surgery, 109 (61.9%) were confirmed node positive on pathology and 67 (38.1%) were downstaged to pN0 at resection. Of the 696 pT1N1 patients, 587 (84.4%) of patients were clinically node-negative (cN0) or unknown nodal status (cNx) initially. Only 109 (15.7%) patients were node-positive at diagnosis (cN1).

DISCUSSION

Lymph node metastasis in gastric adenocarcinoma is the strongest predictor of disease recurrence.[12–17] Adjuvant therapy (AT) decreases recurrence and improves survival in patients with early gastric cancer with positive lymph nodes.[1,2] The recent single-center, retrospective South Korean studies by Kim et al.[4] and Shin et al.[5] found no associated benefit in recurrence free survival in pT1N1 gastric cancer and prompted questions regarding the recommendation to withhold AT in patients with pT1 gastric cancer and low LN burden. However, in this study using a Western patient cohort from the NCDB, adjuvant therapy was associated with a survival benefit even in patients with

minimal lymph node disease. Therefore, the results obtained from the homogeneous patient population found in Kim's and Shin's studies should be cautiously interpreted before extrapolating to more heterogeneous patient populations.

Based on prior trials, the current NCCN guidelines, and our large national review, AT should be offered to Western population patients with pT1 gastric cancer and any degree of lymph node disease who are acceptable risk for systemic therapy.[1–3] This study reinforces that lymph node disease is one of the major risk factors for distant recurrence as described in prior publications, and accurate lymph node assessment remains critical for accurate staging.[18,19] Patients with pT1N1 disease had significantly worse survival compared with pT1N0 disease. Moreover, patients with pN1 disease who received adjuvant therapy had an associated improvement in survival that was more similar to the survival seen in pN0 patients than to pN1 OBS patients. Despite clear recommendations of the NCCN, 47% of this study's pT1N1 patient population did not receive adjuvant therapy. It is unclear why such a large proportion of eligible patients did not receive guideline concordant care. Factors associated with increased receipt of therapy were two positive lymph nodes, distal tumor location, and younger age.

This study demonstrated that retrieval of $\geq$ 15 lymph nodes was associated with improved survival in all patients, reinforcing the need for accurate lymph node status to most accurately stratify the risk of disease recurrence. The NCCN recommends retrieval of at least 15 lymph nodes during surgery to minimize understaging.[3,20] The importance of accurate nodal staging has resulted in the recommendation of formal lymphadenectomy for early gastric cancers.[21] In addition, clinical staging of suspected nodal disease is of limited utility for early-stage cancers. The current study shows that 82.4% of the pT1N1 cohort did not have clinically staged nodal status at diagnosis or were upstaged on final pathology. Of all cN0 or cNx gastric cancers who did not receive neoadjuvant therapy, upstaging at surgical resection occurred in 11.7% of patients. Given the crucial role that lymph node assessment plays in the risk stratification of gastric cancer, there appears to be an opportunity to more fully stage patients at diagnosis and may be a contributing factor resulting in the variation between studies.[22] It is unclear if this limitation in accurate staging is secondary to lack of integration of more sensitive staging modalities, such as diagnostic laparoscopy or positron emission tomography scan, or if it reflects an inadequacy of the current modalities available.[23]

There is an increasing body of literature suggesting a role for localized, endoscopic mucosal resections of early gastric cancer in Eastern patient populations.[24–26] Furthermore, some data suggest endoscopic resection coupled with sentinel lymph node navigation and laparoscopic lymphadenectomy.[27,28] Reinforcing the data presented here, other investigators have demonstrated a lymph node metastasis rate of 4–21% for pT1a tumors and 17–64% for pT1b tumors in Western patient populations.[15,29–35] Given the reported rates of lymph node positivity for early-stage gastric cancer in Western patients, surgical resection with formal lymphadenectomy is considered standard of care to ensure accurate staging and optimal outcomes.

Although it is unclear why differences in the efficacy of adjuvant therapy in pT1N1 gastric cancer are observed between Eastern and Western populations, the role of racial disparities in survival outcomes in gastric cancer cannot be ignored.[8–10,23,29–32] The Kim and Shin studies reflect a homogeneous East Asian patient population in which a lower frequency of lymph node metastasis has been described.[4,33–35] Even when accounting for lymph node status and other clinicopathologic features, Asian race has been shown to be independently associated with improved survival in gastric adenocarcinoma.[8–10,33–35] Shin documented a 5-year survival rate of 90–95% for pT1N1 gastric cancer, which is markedly higher than reported in the present study.[5] This could suggest different underlying biologic processes between races/ethnicities or a result of understaging with less RLN in Western practice. However, in the current study's subset analysis of resected patients with $\geq$ 15 RLN, there remained a significant difference in survival between pT1N0 and pT1N1 patients, suggesting underlying biological differences between the NCDB cohort and the East Asian patient population.

The underlying biologic processes driving racial/ethnic disparities are not fully understood but could be due to other factors including tumor location, *Helicobacter pylori* infections, rates of screening, or socioeconomic factors. Within the current study cohort, Asian patients were the least likely to have proximal tumors, with only 5.7% of tumors in the cardia compared with 47.6% in Non-Hispanic white, 14.2% in Hispanic, and 8.9% in Non-Hispanic black patients ($p < 0.001$). Unfortunately, the NCDB does not report *H. pylori* status or screening. Further research is needed to further classify the factors associated with improved survival in Asian patients.

This study is consistent with prior trials that demonstrate improved survival with adjuvant therapy. The results showing improvement in OS with ACT or ACRT in node-positive patients are similar to findings published from the ARTIST trial that randomized 228 patients with curatively resected gastric cancer with D2 lymph node dissection to receive ACT or ACRT.[36] The trial found no associated improvement in disease-free survival (DFS) with the addition of ACRT in the intention to treat population but did see a significant improvement in subgroup analysis of

lymph node-positive patients.[36] A follow-up trial, ARTIST-II, including curatively resectable gastric cancer with positive lymph nodes is planned.[36]

This study is observational and retrospective in nature and has the expected limitations. However, it was not performed for practice-changing intent but rather to explore the efficacy of standard treatment and compare to recently published results. We hoped to demonstrate the concern with extrapolation of conclusions based on a homogeneous Asian population to that of a heterogeneous Western population. We attempted to limit the impact of inherent bias associated with retrospective reviews through multivariable regression analysis. Although there are known limitations related to administrative databases, the NCDB has more granular reporting of cancer-related variables. We were unable to analyze the relationship between node positivity and the risk for local recurrence in early-stage gastric cancers as the NCDB does not report recurrence data. Additionally, we were unable to confirm tumor stage or histology. We attempted to adjust for this limitation by having strict inclusion criteria of clearly documented stage and histology, but it is not possible to verify what is reported in the NCDB. We could not calculate or report the number lost to follow-up in our analysis. The NCDB reports its accredited centers should obtain a 90%, 5-year, follow-up rate but that in certain cohorts the lost-to-follow-up rate may approach 25%.[37] Finally, we could not account for the heterogeneity of the adjuvant treatment regimens due to the limitations of the NCDB.

In conclusion, lymph node positivity was associated with worse survival in pT1 gastric adenocarcinoma within a large, heterogeneous cohort. Appropriate lymph node staging with $\geq$ 15 lymph node retrieval was associated with improved survival. The administration of adjuvant chemotherapy, with or without concomitant radiation, was independently associated with improved survival when lymph node positivity was present.

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