PATIENT SURVIVAL WITH ypT0N+ FOLLOWING NEOADJUVANT THERAPY IN GASTRIC AND RECTAL CANCERS

PATIENT SURVIVAL WITH ypT0N+ FOLLOWING NEOADJUVANT THERAPY IN GASTRIC AND RECTAL CANCERS

By

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BACKGROUND

Gastric and rectal cancers are common gastrointestinal malignancies worldwide and responsible for a large number of cancer cases and deaths. Gastric cancer was responsible for over 1 million new cancer cases and approximately 769,000 cancer-related deaths in 2020.[1] Similarly, rectal cancer was responsible for 732,210 new cases and 339,022 cancer-related deaths in 2020.[2]

The management of gastric and rectal cancers differs; however, some aspects can be found in common. Patients with early-stage disease can be mainly treated with surgery, while patients with locally advanced disease can be offered neoadjuvant therapy (NAT) before undergoing surgery and/or adjuvant therapy after surgery.[3,4] There are different modalities of the NAT including administering chemotherapy, radiation therapy, or a combination of both. Additionally, there has been a growing interest to use total neoadjuvant therapy (i.e., preoperative chemoradiation plus chemotherapy) for rectal cancer patients.[5]

The pathologic response after NAT was found to be one of the most significant factors of patient survival in both gastric and rectal cancers.[6,7] Previous studies demonstrated that patients who developed pathologic complete response (pCR), also known as ypT0N0, had major improvements in overall survival.[8,9] The American Joint Committee on Cancer (AJCC) has created a ypTNM staging system for gastric cancer patients who underwent NAT followed by surgical resection. However, the AJCC ypTNM staging system does not include ypT0N0 or ypT0N+.[6] In addition, there is still a need to establish a similar staging system for rectal cancer patients who had NAT followed by surgery.

While pCR has extensively been evaluated, less is known about the survival outcomes of gastric and rectal cancer patients who developed ypT0N+.

Patient Survival with ypT0N+ Following Neoadjuvant Therapy in Gastric Cancer

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Abstract

Background

Survival outcomes of gastric cancer patients who developed ypT0N+ remain poorly characterized.

Methods

A survival analysis of the NCDB was conducted on patients with gastric adenocarcinoma who underwent neoadjuvant therapy and surgery.

Results

A total of 7,238 patients were included, of whom 133 were ypT0N+. Achieving ypT0N+ was associated with lower 5-year and 3-year OS than ypT0N0 and ypT1-2N0. There were no differences in 1-year OS between ypT0N+ and ypT0N0 or ypT1-2N0. There were also no differences in 5-year, 3-year, or 1-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+. Developing ypT0N+ was associated with a higher 5-year OS than ypT3-4N+. There were no differences in 3-year or 1-year OS between ypT0N+ and ypT3-4N+.

Conclusion

Developing ypT0N+ was associated with lower 5-year and 3-year OS than ypT0N0 and ypT1-2N0 and a higher 5-year OS than ypT3-4N+.

Keywords: neoadjuvant therapy, gastric cancer, ypT0N+, pathologic response, survival, ypTNM staging.

Introduction

Gastric cancer was responsible for over 1 million new cancer cases and approximately 769,000 cancer-related deaths in 2020, making it the fifth most frequently diagnosed cancer and the fourth leading cause of cancer death worldwide.[1] In the United States (US), 26,259 new cases of gastric cancer and 11,413 deaths were reported in 2020.[2]

Complete surgical resection of gastric cancer is an important element of a curative-intent path in the treatment of this disease. Patients with early-stage gastric cancer (T1a) are candidates for endoscopic resection.[3, 4] In more advanced disease (≥T1b), complete resection with either total or subtotal gastrectomy as well as lymphadenectomy are recommended.[4] Many patients present with locally advanced disease, for which surgery alone may be insufficient for cure.[5] For these patients, there has been a persistent increase in the utilization of neoadjuvant therapy (NAT). Based on a previous national study, the use of NAT increased from 25.9% in 2003 to 46.3% in 2012 among gastric cancer patients.[6] A possible reason for this includes patient intolerance to adjuvant therapies following major surgery, which results in incomplete multimodal therapy.[7] In addition, NAT allows for tumor downstaging, an increase in negative-margin resections, nodal sterilization, and provides a temporal test of tumor biology and disease aggressiveness.

The change in the treatment paradigm to include NAT has required modification of the American Joint Committee on Cancer (AJCC) staging of gastric cancer.[8] The eighth edition includes a "yp" staging system for gastric cancer patients who underwent NAT followed by surgical resection.[8] Response to NAT, reflected by a lower yp stage, was shown to be one of the most important prognostic factors in resected gastric cancer patients.[9,10] However, the current AJCC yp staging

system does not include ypT0. Previous studies demonstrated that gastric cancer patients who developed pathologic complete response (pCR), also known as ypT0N0, exhibited dramatic improvements in overall survival (OS).[11] While pCR has recently been evaluated, less is known about the survival of gastric cancer patients who had a complete response in the primary tumor but with persistent nodal disease (ypT0N+). Thus, we chose to examine the survival of ypT0N+ patients following NAT and surgery, to better characterize the survival of this unique category. Specifically, 5-year OS was examined as the primary outcome, and 3-year and 1-year OS were included as secondary outcomes, which may be pertinent in patients with shorter-term survival.

Methods

Study Design and Population

The National Cancer Database (NCDB) was used to describe the survival of gastric cancer patients who had surgery between 2004 and 2016. The NCDB is co-sponsored by the American Cancer Society and the American College of Surgeons Commission on Cancer. It is a hospital-based database that collects data from more than 1500 Commission on Cancer–accredited programs in the US. The NCDB captures data for more than 70.0% of all newly diagnosed cancer cases in the US each year. So far, it has approximately 34 million records from hospital cancer registries across the US, making it one of the largest and most representative databases in the world.[12]

Inclusion criteria included patients who underwent surgical resection with subsequent histology of gastric adenocarcinoma among patients who received NAT that consisted of either chemotherapy alone or chemotherapy and radiation therapy. Confirmation of the diagnosis of gastric adenocarcinoma was obtained using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3).[13] Histology codes 8010, 8140, 8142, 8144, 8145, 8480, and 8560 were utilized.

Exclusion criteria included unknown tumor size and extent, unknown nodal status, metastatic disease, recurrent disease, clinical stage 0, unknown clinical stage, and mortality within 30 days of the surgical operation since this was less likely due to disease progression. Figure 1 gives an overview of the selection criteria for the study cohort. This study was exempt from Institutional Review Board as the database involved deidentified data.

Selected Variables

Patient demographics included age, gender (male or female), race/ethnicity (white or non-white), and Charlson-Deyo score. Tumor-related information included year of diagnosis, clinical stage, tumor size and extent, tumor location with respect to the gastroesophageal junction, tumor grade, surgical resection margins, number of lymph nodes harvested, and the number of positive lymph nodes. Considering changes in trends of clinical practice that occurred during the study period, the variable of the year of diagnosis was categorized into two distinct groups, including 2004 to 2009 and 2010 to 2016. These groups were selected because of the increased nationwide utilization of NAT in 2010 within the database.

Treatment-related variables included type of NAT (chemotherapy alone or chemotherapy and radiation therapy) as well as receipt and type of adjuvant therapy. The NCDB does not include variables on specific comorbidities nor chemotherapy regimens received. In addition, the NCDB does not report additional outcomes such as disease-specific survival or disease recurrence.

Outcomes

In keeping with prior reporting, patients were categorized into six pathologic groups: (i) ypT0N+ (ii) ypT0N0 (iii) ypT1-2N0 (iv) ypT3-4N0 (v) ypT1-2N+ (vi) ypT3-4N+.[14] The primary outcome measured was 5-year OS. Secondary outcomes included 3-year and 1-year OS for each category.

Statistical Analyses

Descriptive statistics were utilized for patient characteristics. For continuous, normally distributed data, the mean and standard deviation (SD) were used with a comparison of each of the five categories with ypT0N+ conducted using a two-sample t-test. For continuous, non-normally distributed data, median and interquartile range (IQR) were used with a comparison of each group with ypT0N+ conducted using the Mann–Whitney U test. For categorical data, results were reported using counts (n) and percentages (%) with comparisons with ypT0N+ made using Pearson's Chi-square test.

The Kaplan-Meier method was used to report the 5-year OS of each pathologic category and the log-rank test was utilized to compare 5-year, 3-year, and 1-year OS of each of the five categories with ypT0N+. This was followed by running univariable and multivariable Cox proportional hazard regression to analyze OS with adjustment of other covariates including age, gender, race, Charlson-Deyo score, year of diagnosis, clinical stage, number of lymph nodes harvested, positive nodal burden, tumor location, surgical resection margins, tumor grade, type of NAT, and receipt and type of additional adjuvant therapy. Results of the multivariable adjusted Cox analysis were reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values. Missing data were handled using a complete case analysis approach. All statistical analyses were performed using Stata software version 16.0 (StataCorp, College Station, Texas, United States).

Results

A total of 7,238 patients with gastric cancer were included, of whom 133 patients developed ypT0N+ (table 1). There was a greater proportion of males across all pathologic categories ranging from 75.8% to 88.0%. The median number of lymph nodes harvested [IQR] ranged from 15 [10, 22] in node-negative categories to 18 [12, 25] in ypT3-4N+. The median number of lymph nodes harvested for ypT0N+ was 17 [12, 23]. The median number of positive lymph nodes for ypT0N+ was 1 [1, 2]. The proportion of patients who had gastro-esophageal junction tumors ranged from 65.0% in ypT3-4N+ to 87.2% in ypT0N+.

Among ypT0N+ patients, 35 (26.3%) had moderately differentiated tumors and 71 (53.4%) had poorly differentiated tumors. Neoadjuvant chemotherapy and radiation therapy were administered to 108 patients (81.2%) with ypT0N+. The proportion of patients who received adjuvant chemotherapy ranged from 9.7% (in ypT0N0) to 23.4% (in ypT3-4N+). Adjuvant chemotherapy was administered in 26 (19.5%) ypT0N+ patients. Patients with ypT0N+ had a lower likelihood of receiving adjuvant therapy than patients with ypT3-4N+ disease.

Achieving ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0 (35.6% vs. 63.6% and 60.2%, respectively; $p<0.05$) (figure 2). In addition, developing ypT0N+ was associated with a lower 3-year OS than ypT0N0 and ypT1-2N0 (56.4% vs. 74.4% and 71.5%, respectively; $p<0.05$) (table 2). There were no differences in 1-year OS between ypT0N+ and ypT0N0 or ypT1-2N0. There were also no differences in 5-year, 3-year, or 1-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+.

Having ypT0N+ disease was associated with improved 5-year OS compared with ypT3-4N+ (35.6% vs. 21.3%; $p<0.05$). However, there were no differences in 3-year or 1-year OS between ypT0N+ and ypT3-4N+.

On the multivariable Cox regression, developing ypT0N0 and ypT1-2N0 was associated with 50.0% and 40.0% decreases in mortality (HR=0.50, 95% CI: 0.37-0.67; $p<0.001$ and HR=0.60, 95% CI: 0.46-0.80; $p<0.001$, respectively) compared with ypT0N+ (table 3). On the other hand, having ypT3-4N+ was associated with a 37.0% increase in mortality (HR=1.37, 95% CI: 1.04-1.79; $p=0.021$).

On multivariable analysis, age (HR=1.05, 95% CI: 1.02-1.08; $p=0.002$) and having 7 or more positive lymph nodes (HR=3.28, 95% CI: 1.04-10.33; $p=0.042$) were associated with a decrease in OS (table 4). There was no difference in OS among ypT0N+ patients who received neoadjuvant chemotherapy and radiation therapy and those who had neoadjuvant chemotherapy.

Discussion

Survival outcomes of gastric cancer patients who developed ypT0N+ following NAT remain poorly characterized in the literature. This study showed that for patients diagnosed with gastric adenocarcinoma who underwent NAT followed by surgical resection, achieving ypT0N+ was associated with a lower 5-year and 3-year OS than ypT0N0 and ypT1-2N0. However, ypT0N+ disease was associated with an improved 5-year OS compared with ypT3-4N+. There were no differences in 5-year, 3-year, or 1-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+, to which the reference group was most comparable. Finally, age and having 7 or more positive lymph nodes were associated with a decrease in the OS of ypT0N+ patients.

The eighth edition of the AJCC manual evolved to include a staging system for gastric cancer patients who received NAT (ypTNM staging). However, the staging system does not include ypT0N0 or ypT0N+.[8] Patients with pCR (ypT0N0) have already been shown to exhibit improved survival compared with patients with incomplete pathologic responses.[15] However, only few studies have evaluated the survival of ypT0N+ patients.[9, 11] Our findings describe a distinct group of patients with survival characteristics that merit consideration for inclusion in future versions of the AJCC staging system for gastric cancer patients who had NAT followed by surgical resection. In addition, our study may provide helpful prognostic information to counsel patients with residual nodal involvement after complete tumor response following NAT and surgical resection.

In keeping with findings shown in this study, a previous study (n=77) conducted at the MD Anderson Cancer Center compared survival outcomes of 67 patients with ypT0N0 and 10 patients with ypT0N+.[11] The authors found that developing ypT0N0 status was associated with a

substantially higher 5-year OS than ypT0N+ (68.8% vs. 22.9%). Similarly, Ikoma and colleagues showed that patients with ypT0N0 were associated with improved 5-year and 3-year OS than patients with ypT0N+ (70.0% vs. 23.0% and 82.0% vs. 23.0%, respectively).[9] Survival outcomes of ypT0N+ patients were substantially lower and were largely attributed to the advanced tumor characteristics at presentation, for which concomitant organ resections were required among their patient cohort. Incidentally, the authors also reported no difference in survival between ypT0N0 and yp stage I patients, i.e., patients with ypT1-2N0 or ypT1N1 (5-year OS: 70.0% vs. 74.0%). Therefore, the authors concluded that it would be feasible to combine pCR patients with yp stage I patients in future iterations of the AJCC staging system following NAT.[9] Similar results were also shown in a study for gastric cancer patients from China.[16]

In our study, we found that achieving ypT0N+ was associated with a substantially lower 5-year OS than ypT1-2N0. This was consistent with findings reported by Ikoma and colleagues who found that 5-year OS of ypT1N0 was 74.0% and the 5-year OS of ypT2N0 was 68.0% while that of ypT0N+ was 23.0%.[9] In a separate report by Kim and colleagues, the authors demonstrated that survival of ypT0N+ esophageal cancer patients was similar to that of patients with ypT2-3N0 or ypT1-2N1.[17] Verlato and colleagues reported that persistent positive nodal status after NAT was associated with poor OS, irrespective of the pathologic response in the primary tumor (tumor regression grade).[18] It appears that persistent nodal positivity consistently infers a greater prognostic role compared with tumor size, including a fully disappeared primary tumor (T0).

In a study by Li and colleagues, the authors examined the importance of tumor size compared with nodal stage and specifically demonstrated that both ypT and ypN were independent predictors of

gastric cancer patients' survival. However, the authors were able to demonstrate that ypN stage was of more critical prognostic value than ypT stage. The authors found no survival differences between consecutive ypT stages, except for ypT4a and ypT4b. On the other hand, the authors detected differences in OS between ypN1 and ypN2, and between ypN2 and ypN3 patients.[16] Similarly, a previous retrospective cohort study that incorporated both MD Anderson Cancer Center data (n=175) and NCDB data (n=3,200) revealed that the survival of patients with node-negative gastric cancer was not influenced by the ypT stage.[19] In fact, there was no detectable difference in OS between patients with pCR (ypT0N0) and those with ypT1-3N0 disease, confirming potentially the diminished role of ypT in determining OS among patients who achieved ypN0 status.

In 2006, the results of the MAGIC trial were published. That trial showed that among gastric cancer patients who were eligible for surgery, perioperative chemotherapy reduced tumor size and stage and substantially improved progression-free and OS.[4] In 2011, the primary report of the CROSS trial was published. It found that neoadjuvant chemoradiotherapy increased survival among patients with potentially curable esophageal or esophagogastric-junction cancers.[4]

Our study found that most patients across all pathologic categories received neoadjuvant chemotherapy and radiation therapy. Ikoma and colleagues demonstrated that neoadjuvant chemoradiation therapy was associated with a higher likelihood of achieving ypT0 than with neoadjuvant chemotherapy (OR= 2.28, 95% CI: 1.76–2.95; $p< 0.001$).[20] Similarly, Allen and colleagues found that patients who received both neoadjuvant chemotherapy and chemoradiation developed pCR (ypT0N0) more frequently than patients who received neoadjuvant chemotherapy alone (27.7% vs. 1.5%; $p<0.001$).[21] Interestingly, there were no differences in OS between the

treatment arms in either study. This is in keeping with findings from our study showing no difference in OS among ypT0N+ patients who received neoadjuvant chemotherapy and radiation therapy vs. neoadjuvant chemotherapy alone.

This study has some limitations. First, the NCDB does not provide data on disease recurrence and disease-specific survival, which could be of interest in patients with ypT0N+. Second, there was likely a variation in neoadjuvant strategies based on time-periods, although this was counteracted in part by dividing the study into two periods that were included in the multivariable analysis. Third, the relatively small number of ypT0N+ patients may have limited the ability to detect some statistical differences and the generalizability of the study. Finally, the retrospective nature of the study may raise the potential of residual confounding.

Conclusion

In patients with gastric adenocarcinoma who undergo NAT followed by surgical resection, achieving ypT0N+ was associated with a lower 5-year and 3-year OS than ypT0N0 and ypT1-2N0. On the other hand, ypT0N+ disease was associated with improved 5-year OS compared with ypT3-4N+. There were no differences in 5-year, 3-year, or 1-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+. Age and having 7 or more positive lymph nodes were associated with a decrease in the OS of ypT0N+ patients. Future inclusion of both ypT0N0 and ypT0N+ into the AJCC ypTNM staging should be considered.

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FIGURES AND TABLES

Figure (1): Overview of the selection criteria for the study cohort

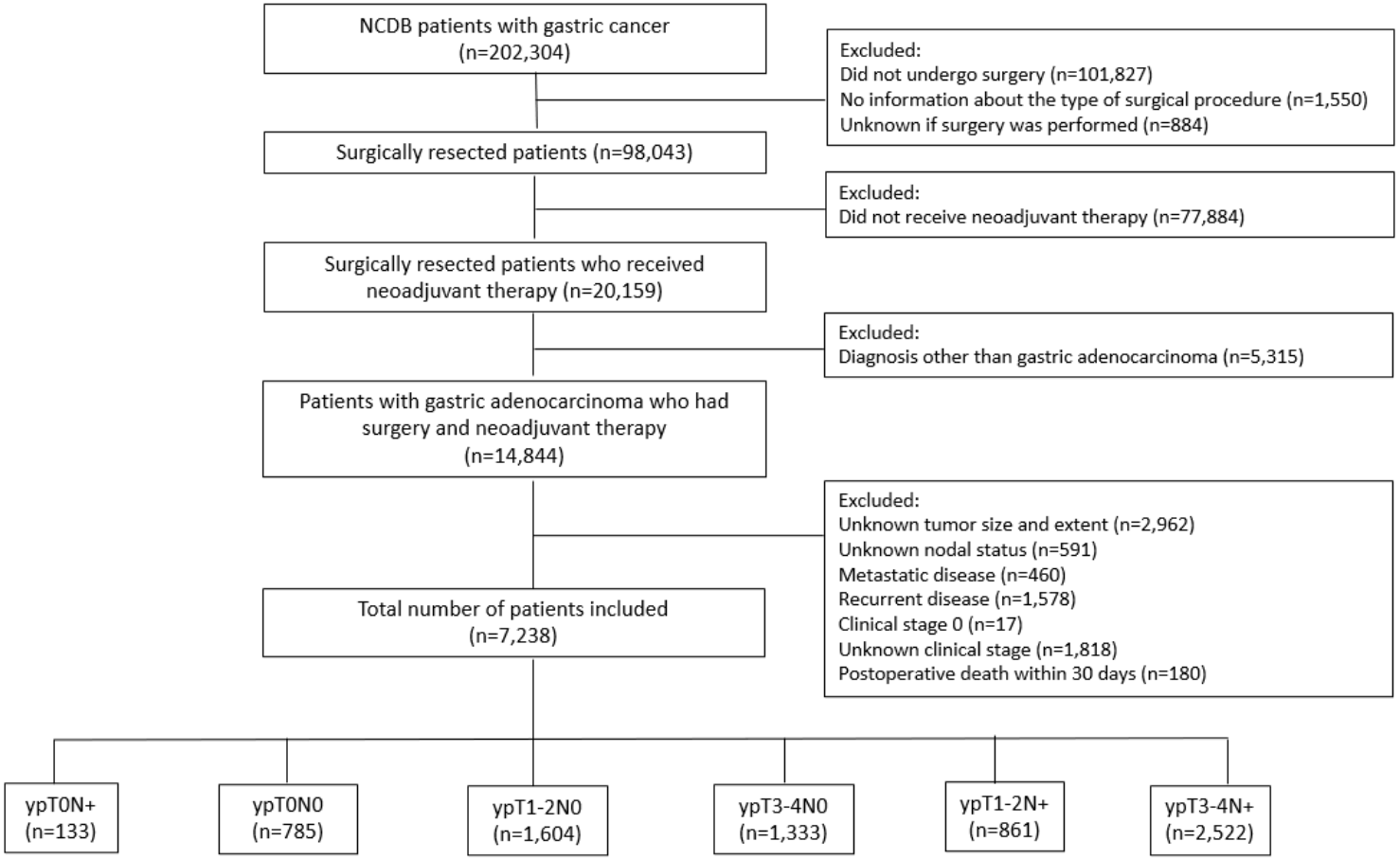
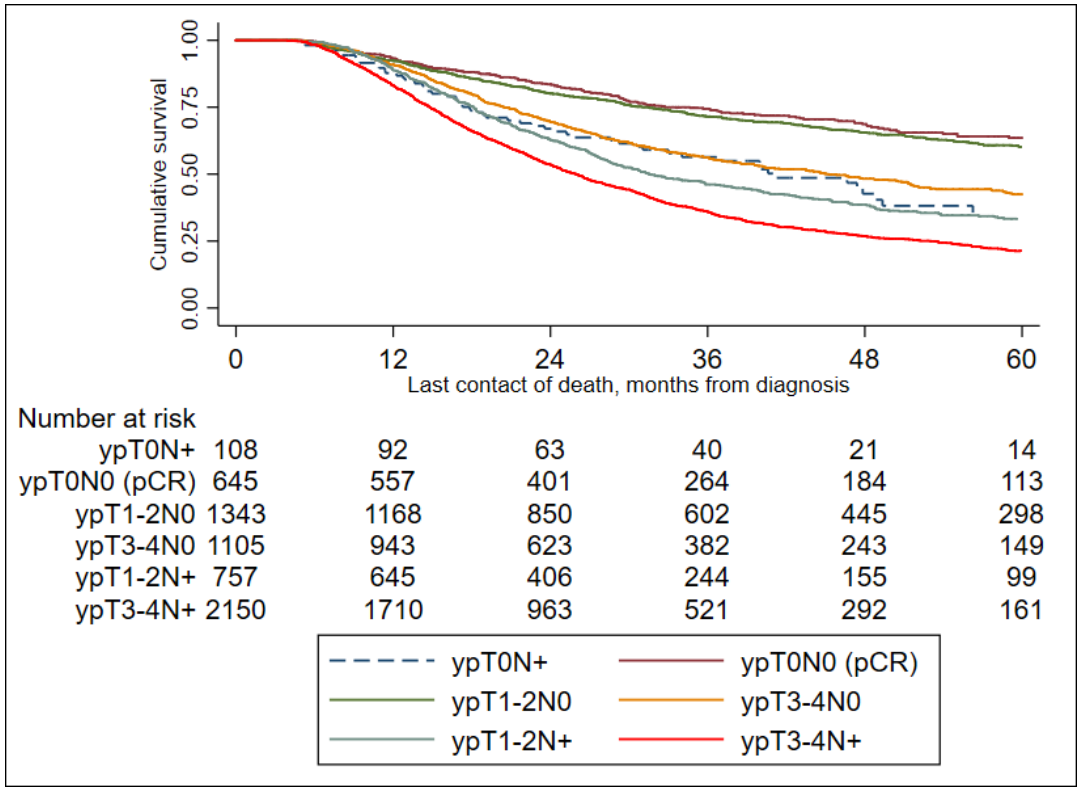


Figure (2): 5-year overall survival of gastric cancer patients. Achieving ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0 ($p<0.05$). However, it was associated with improved 5-year OS compared with ypT3-4N+ ($p<0.05$). There was no associational difference in 5-year OS comparing ypT0N+ with ypT3-4N0 and ypT1-2N+ ($p>0.05$).



pCR= pathologic complete response

Table 1: Characteristics of gastric cancer patients.

Characteristic	**ypT0N+ (n=133)**	**ypT0N0 (pCR) (n=785)**	**ypT1-2N0 (n=1604)**	**ypT3-4N0 (n=1333)**	**ypT1-2N+ (n=861)**	**ypT3-4N+ (n=2522)**
Mean age± SD	60.9± 10.0	62.8± 9.9*	62.6± 10.2	61.6± 10.5	62.2± 10.1	60.9± 11.1
Male gender, n (%)	117 (88.0)	649 (82.7)	1280 (79.8)*	1014 (76.1)*	706 (82.0)	1912 (75.8)*
White race, n (%)	119 (89.5)	703 (89.6)	1387 (86.5)	1151 (86.3)	734 (85.2)	2061 (81.7)*
Year of diagnosis, n (%)				*	*	
2004-2009	17 (12.8)	72 (9.2)	228 (14.2)	100 (7.5)	172 (20.0)	234 (9.3)
2010-2016	116 (87.2)	713 (90.8)	1376 (85.8)	1233 (92.5)	689 (80.0)	2288 (90.7)
Charlson-Deyo score, n (%)						
0	101 (75.9)	554 (70.6)	1101 (68.6)	960 (72.0)	620 (72.0)	1801 (71.4)
1	28 (21.1)	163 (20.8)	371 (23.1)	278 (20.9)	179 (20.8)	569 (22.6)
≥ 2	4 (3.0)	68 (8.6)	132 (8.3)	95 (7.1)	62 (7.2)	152 (6.0)
Clinical stage, n (%)		*	*	*		
I	11 (8.3)	124 (15.8)	362 (22.6)	122 (9.2)	105 (12.2)	168 (6.7)
II	43 (32.3)	310 (39.5)	714 (44.5)	697 (52.3)	341 (39.6)	976 (38.7)
III	79 (59.4)	351 (44.7)	528 (32.9)	514 (38.5)	415 (48.2)	1378 (54.6)
Median lymph nodes removed [IQR]	17 [12, 23]	15 [10, 22]	15 [10, 22]*	15 [9, 22]*	17 [12, 25]	18 [12, 25]
Median positive lymph nodes [IQR]	1 [1, 2]	0*	0*	0*	2 [1, 4]*	3 [2, 7]*
Number of positive lymph nodes¥, n (%)		*	*	*	*	*
N0 (no regional lymph node metastasis)	0	785 (100.0)	1604 (100.00	1333 (100.0)	0	0
N1 (metastasis in one or two regional lymph nodes)	102 (76.7)	0	0	0	523 (60.7)	972 (38.5)
N2 (metastasis in three to six regional lymph nodes)	23 (17.3)	0	0	0	243 (28.3)	886 (35.2)
N3 (metastasis in seven or more regional lymph nodes)	8 (6.0)	0	0	0	95 (11.0)	664 (26.3)
Gastro-esophageal junction tumor, n (%)	116 (87.2)	652 (83.1)	1211 (75.5)*	972 (72.9)*	641 (74.4)*	1640 (65.0)*
Grade, n (%)		*	*	*	*	*
Well-differentiated	1 (0.8)	33 (4.2)	94 (5.9)	48 (3.6)	31 (3.6)	56 (2.2)
Moderately differentiated	35 (26.3)	283 (36.1)	698 (43.5)	452 (33.9)	267 (31.0)	705 (28.0)
Poorly differentiated	71 (53.4)	334 (42.5)	666 (41.5)	693 (52.0)	494 (57.4)	1555 (61.7)
Unknown	26 (19.5)	135 (17.2)	146 (9.1)	140 (10.5)	69 (8.0)	206 (8.1)
Surgical margins, n (%)				*	*	*
Negative	133 (100.0)	783 (99.7)	1555 (96.9)	1219 (91.4)	800 (92.9)	2082 (82.5)
Positive	0	0	23 (1.4)	72 (5.4)	23 (2.7)	252 (10.0)
Unknown	0	2 (0.3)	26 (1.7)	42 (3.2)	38 (4.4)	188 (7.5)
Type of neoadjuvant therapy, n (%)			*	*	*	*
Chemotherapy	25 (18.8)	181 (23.1)	554 (34.5)	464 (34.8)	317 (36.8)	1209 (47.9)
Chemotherapy and radiation therapy	108 (81.2)	604 (76.9)	1050 (65.5)	869 (65.2)	544 (63.2)	1313 (52.1)
Adjuvant therapy, n (%)		*				*
None	103 (77.4)	702 (89.4)	1311 (81.7)	1061 (79.6)	622 (72.2)	1624 (64.4)
Chemotherapy	26 (19.5)	76 (9.7)	246 (15.4)	214 (16.1)	189 (22.0)	589 (23.3)
Radiation therapy	1 (0.8)	5 (0.6)	32 (2.0)	35 (2.6)	23 (2.7)	125 (5.0)

Chemotherapy and radiation therapy	3 (2.3)	2 (0.3)	15 (0.9)	23 (1.7)	27 (3.1)	184 (7.3)

pCR= pathologic complete response, n= number of patients, SD= standard deviation

*The p-value is less than 0.05 in reference to ypT0N+ category.

¥Based on the American Joint Committee on Cancer (AJCC) categorization.

Table (2): Survival of gastric cancer patients according to pathological category.

Pathologic category	1-year OS (%)	3-year OS (%)	5-year OS (%)
ypT0N0 (pCR)	93.2	74.4*	63.6*
ypT1-2N0	92.3	71.5*	60.2*
ypT3-4N0	90.8	56.2	42.5
ypT0N+	87.8	56.4	35.6
ypT1-2N+	88.7	46.1	33.3
ypT3-4N+	83.1	35.9	21.3*

OS= overall survival, pCR= pathologic complete response.

* Log-rank test p-value is less than 0.05 in reference to ypT0N+ category.

Table (3): univariable and multivariable analysis of patient characteristics and their association with overall survival.

Variable	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.01	1.002- 1.009	<0.001	1.01	1.007- 1.014	<0.001
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.09	0.99- 1.19	0.06	1.03	0.94- 1.13	0.47
Race						
Non-white	Ref	Ref	Ref	Ref	Ref	Ref
White	1.33	1.18- 1.49	<0.001	1.29	1.15- 1.46	<0.001
Year of diagnosis						
2004-2009	Ref	Ref	Ref	Ref	Ref	Ref
2010-2016	0.97	0.88- 1.06	0.49	0.92	0.83- 1.01	0.08
Charlson-Deyo score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.19	1.09- 1.29	<0.001	1.16	1.06- 1.26	0.001
≥ 2	1.07	0.93- 1.24	0.34	1.09	0.94- 1.26	0.26
Clinical stage						
I	Ref	Ref	Ref	Ref	Ref	Ref
II	1.29	1.14- 1.46	<0.001	1.10	0.97- 1.26	0.15
III	1.67	1.47- 1.88	<0.001	1.23	1.08- 1.39	0.002
Pathologic category						
ypT0N+	Ref	Ref	Ref	Ref	Ref	Ref
ypT0N0 (pCR)	0.46	0.34- 0.62	<0.001	0.50	0.37- 0.67	<0.001
ypT1-2N0	0.53	0.40- 0.69	<0.001	0.60	0.46- 0.80	<0.001
ypT3-4N0	0.87	0.66- 1.14	0.31	0.96	0.73- 1.27	0.78
ypT1-2N+	1.09	0.83- 1.44	0.53	1.08	0.82- 1.43	0.57
ypT3-4N+	1.53	1.18- 1.99	0.002	1.37	1.04- 1.79	0.021
Number of lymph nodes removed	0.99	0.987- 0.995	<0.001	0.98	0.977- 0.985	<0.001
Number of positive lymph nodes	1.07	1.06- 1.08	<0.001	1.06	1.05- 1.07	<0.001
Gastro-esophageal junction tumor						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.14	1.05- 1.24	0.002	1.05	0.94- 1.17	0.42
Grade						
Well-differentiated	Ref	Ref	Ref	Ref	Ref	Ref
Moderately differentiated	1.13	0.91- 1.40	0.25	1.12	0.91- 1.39	0.29
Poorly differentiated	1.61	1.30- 1.98	<0.001	1.45	1.17- 1.79	0.001
Surgical margins						
Negative	Ref	Ref	Ref	Ref	Ref	Ref
Positive	2.36	2.07- 2.69	<0.001	1.61	1.40- 1.85	<0.001
Type of neoadjuvant therapy						
Chemotherapy	Ref	Ref	Ref	Ref	Ref	Ref
Chemotherapy and radiation therapy	1.16	1.08- 1.25	<0.001	1.22	1.10- 1.35	<0.001
Adjuvant therapy						
None	Ref	Ref	Ref	Ref	Ref	Ref
Chemotherapy	0.92	0.84- 1.01	0.07	0.82	0.74- 0.90	<0.001
Radiation therapy	1.30	1.09- 1.57	0.005	1.19	0.98- 1.45	0.08
Chemotherapy and radiation therapy	1.23	1.03- 1.48	0.022	0.89	0.74- 1.08	0.25

HR= hazard ratio, CI= confidence interval, pCR= pathologic complete response.

Table (4): Subgroup survival analysis of ypT0N+ patients' characteristics and their association with overall survival.

Variable	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.05	1.01- 1.08	0.004	1.05	1.02- 1.08	0.002
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.72	0.35- 1.48	0.38	1.06	0.45- 2.54	0.89
Race						
Non-white	Ref	Ref	Ref	Ref	Ref	Ref
White	0.61	0.28- 1.37	0.23	0.62	0.23- 1.66	0.34
Year of diagnosis						
2004-2009	Ref	Ref	Ref	Ref	Ref	Ref
2010-2016	0.67	0.36- 1.25	0.21	0.82	0.39- 1.70	0.59
Charlson-Deyo score						
0	Ref	Ref	Ref	Ref	Ref	Ref
≥ 1	0.69	0.36- 1.34	0.27	0.79	0.37- 1.66	0.53
Clinical stage						
I	Ref	Ref	Ref	Ref	Ref	Ref
II	0.87	0.34- 2.19	0.76	0.43	0.12- 1.54	0.20
III	0.73	0.30- 1.75	0.48	0.40	0.12- 1.35	0.14
Number of lymph nodes removed	0.98	0.94- 1.01	0.14	0.98	0.95- 1.02	0.30
Number of positive lymph nodes						
N1 (metastasis in one or two regional lymph nodes)	Ref	Ref	Ref	Ref	Ref	Ref
N2 (metastasis in three to six regional lymph nodes)	1.55	0.80- 3.03	0.20	1.53	0.71- 3.29	0.27
N3 (metastasis in seven or more regional lymph nodes)	2.26	0.79- 6.46	0.13	3.28	1.04- 10.33	0.042
Gastro-esophageal junction tumor						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.84	0.39- 1.78	0.65	0.57	0.17- 1.83	0.34
Type of neoadjuvant therapy						
Chemotherapy	Ref	Ref	Ref	Ref	Ref	Ref
Chemotherapy and radiation therapy	1.04	0.54- 2.02	0.90	2.27	0.77- 6.69	0.14
Adjuvant therapy						
None	Ref	Ref	Ref	Ref	Ref	Ref
Chemotherapy	1.24	0.67- 2.28	0.50	1.23	0.63- 2.41	0.54
Radiation therapy	5.22	0.69- 39.26	0.11	1.92	0.14- 26.03	0.62
Chemotherapy and radiation therapy	0.94	0.13- 6.86	0.95	0.95	0.08- 10.64	0.97

HR= hazard ratio, CI= confidence interval

SUPPLEMENTARY MATERIALS

Supplementary table (1): Comparison of the characteristics of the included vs. excluded patients.

Characteristic	Included Patients (n=7238)	Excluded Patients (n=195066)	p-value
Mean age± SD	61.8± 10.6	67.3± 13.8	<0.001
Male gender, n (%)	5678 (78.4)	119734 (61.4)	<0.001
White race, n (%)	6155 (85.0)	147313 (75.5)	<0.001
Year of diagnosis, n (%)			
2004-2009	823 (11.4)	82085 (42.1)	<0.001
2010-2016	6415 (88.6)	112981 (57.9)	
Charlson-Deyo score, n (%)			
0	5137 (71.0)	132847 (68.1)	<0.001
1	1588 (21.9)	42424 (21.7)	
≥ 2	513 (7.1)	19795 (10.2)	
Clinical stage, n (%)			
I	892 (12.3)	30802 (15.8)	<0.001
II	3081 (42.6)	17134 (8.8)	
III	3265 (45.1)	17276 (8.9)	
Median lymph nodes removed [IQR]	16 [11, 23]	0 [0, 12]	<0.001
Median positive lymph nodes [IQR]	0 [0, 3]	1 [0, 5]	
Number of positive lymph nodes[¥], n (%)			
N0 (no regional lymph node metastasis)	3722 (51.4)	157358 (80.7)	<0.001
N1 (metastasis in one or two regional lymph nodes)	1597 (22.1)	13419 (6.9)	
N2 (metastasis in three to six regional lymph nodes)	1152 (15.9)	10741 (5.5)	
N3 (metastasis in seven or more regional lymph nodes)	767 (10.6)	13548 (6.9)	
Gastro-esophageal junction tumor, n (%)	5232 (72.3)	63516 (32.6)	<0.001
Grade, n (%)			
Well-differentiated	263 (3.6)	14602 (7.5)	<0.001
Moderately differentiated	2440 (33.7)	40161 (20.6)	
Poorly differentiated	3813 (52.7)	92824 (47.6)	
Unknown	722 (10.0)	47479 (24.3)	
Surgical margins, n (%)			
Negative	6572 (90.8)	174708 (89.6)	<0.001
Positive	370 (5.1)	8002 (4.1)	
Unknown	296 (4.1)	12356 (6.3)	
Type of neoadjuvant therapy, n (%)			
Chemotherapy	2750 (38.0)	43376 (22.2)	<0.001
Chemotherapy and radiation therapy	4488 (62.0)	28354 (14.5)	
Adjuvant therapy, n (%)			
None	5423 (74.9)	102974 (52.8)	<0.001
Chemotherapy	1340 (18.5)	47709 (24.5)	
Radiation therapy	221 (3.1)	6720 (3.4)	
Chemotherapy and radiation therapy	254 (3.5)	30012 (15.4)	

pCR= pathologic complete response, n= number of patients, SD= standard deviation

[¥]Based on the American Joint Committee on Cancer (AJCC) categorization.

Patient Survival with ypT0N+ Following Neoadjuvant Therapy in Rectal Cancer

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Abstract

Background

Following neoadjuvant therapy, pathologic analysis of rectal cancer resected specimens may show a complete response in the primary tissue cancer with residual tumor in the lymph nodes (ypT0N+).

Objectives

To describe the 5-year overall survival and factors associated with survival of ypT0N+ patients with rectal cancer who had neoadjuvant therapy followed by surgery and to compare these patients' survival to patients in other pathologic categories.

Design

We conducted a retrospective analysis.

Settings

We used the National Cancer Database.

Patients

We identified patients with rectal adenocarcinoma who underwent total neoadjuvant therapy or neoadjuvant chemoradiation followed by surgery between 2006 and 2016. Besides ypT0N+, 5 pathologic categories were identified: ypT0N0, ypT1-2N0, ypT3-4N0, ypT1-2N+, and ypT3-4N+.

Main Outcome Measure

Five-year overall survival.

Results

We included 32,843 patients with rectal adenocarcinoma. A total of 374 patients developed ypT0N+, of whom 197 (52.7%) received total neoadjuvant therapy.

Among patients who received total neoadjuvant therapy, developing ypT0N+ was associated with a lower 5-year overall survival than ypT0N0 and ypT1-2N0. However, ypT0N+ disease was associated with a higher 5-year overall survival than ypT3-4N+. There were no differences in 5-year overall survival between ypT0N+ and ypT3-4N0 or ypT1-2N+. Similar findings were noticed among patients who received neoadjuvant chemoradiation and adjuvant chemotherapy.

For patients with ypT0N+, age, male gender, Charlson-Deyo score of ≥2, and having ≥4 positive lymph nodes were all associated with a decrease in overall survival. There was no difference in the overall survival in ypT0N+ patients who received either neoadjuvant modality.

Limitations

Limitations include the retrospective nature of study, lack of variables describing the chemotherapy and radiation regimens used, and paucity of data on disease-specific survival or recurrence.

Conclusions

Developing ypT0N+ was associated with a lower 5-year overall survival than ypT0N0 and ypT1-2N0. However, it was associated with a higher 5-year overall survival than ypT3-4N+.

Keywords: Neoadjuvant therapy, rectal cancer, ypT0N+, pathologic response, overall survival.

Introduction

Rectal cancer is one of the most common cancers worldwide with 732,210 new cases and 339,022 deaths in 2020.[1] In the United States, 43,340 new cases and 53,200 deaths (combined with colon cancer) were estimated in 2020.[2]

Patients with localized rectal cancer (stage I) are primarily treated with surgical resection. On the other hand, patients with locally advanced rectal cancer (stage II and III) have traditionally undergone preoperative chemoradiation (CRT) followed by total mesorectal excision and adjuvant chemotherapy.[3] However, a growing trend has been noticed to use chemotherapy in conjunction with (before or after) preoperative CRT and has been termed total neoadjuvant therapy (TNT). This treatment strategy mainly emerged because of the poor tolerance of adjuvant chemotherapy.[4]

Neoadjuvant therapy (NAT) of rectal cancer has some advantages, including downstaging of the primary tumor, increasing sphincter preservation rates, and ensuring receipt of multimodal therapy. However, the extent of tumor response varies among patients and the resultant pathologic T and N category (ypTN) of the surgical specimen is an important determinant of patient prognosis.[5]

Pathologic complete response, also known as ypT0N0, is defined as having no histological evidence of tumor in the tissue after surgery, and complete disappearance of potential lymph node metastases. The term ypT0N+ is used when the pathology demonstrates a complete response in the primary tissue with residual tumor seen only in the adjacent lymph nodes.[6] Pathologic downstaging after NAT was shown to be one of the most important prognostic factors for rectal

cancer patients.[7-9] Previous studies found that rectal cancer patients who developed ypT0N0 had dramatic improvements in overall survival (OS).[7, 10]

Little is known about the survival outcome of surgically resected patients with rectal cancer who developed ypT0N+, which is currently unaccounted for in staging systems. Our study aimed to describe the 5-year OS of ypT0N+ patients and the factors that are associated with their survival. It also aimed to compare the 5-year OS of ypT0N+ with other pathologic categories.

Materials and Methods

Study Design and Population

The National Cancer Database (NCDB) was used retrospectively to describe the prognosis of rectal cancer patients between 2006 and 2016. The NCDB is jointly sponsored and maintained by the American College of Surgeons Commission on Cancer and the American Cancer Society. It is a hospital-based database that collects data from about 1500 Commission on Cancer–accredited programs in the United States. The NCDB reports approximately 70.0% of cancer cases in the United States annually.[11]

Only patients who ultimately had surgical resection preceded by NAT and subsequent histological diagnosis of rectal adenocarcinoma were included in the study. The NAT modality received was either TNT or CRT. TNT involves the administration of chemotherapy and CRT prior to surgery. On the other hand, the included patients who had received the traditional CRT also had adjuvant systemic chemotherapy. The diagnosis of rectal adenocarcinoma was confirmed using the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3).[12] The following histology codes were used: 8140, 8210, 8263, 8480, 8010, 8261, 8481, and 8490.

Patients were excluded if they had unknown tumor size and extent, unknown nodal status, metastatic disease, recurrent disease, and clinical stage 0 or unknown clinical stage. In addition, patients were excluded if mortality occurred within 30 days of the operation since this was less likely due to disease progression. Figure 1 gives an overview of the selection criteria for the study cohort. This study was exempt from Institutional Review Board as the database involved deidentified data.

Selected Variables

Patient demographics included age, gender (male or female), race/ethnicity (white or non-white), and Charlson-Deyo score. Tumor-related information included year of diagnosis, grade, surgical margins, tumor size and extent, number of lymph nodes that were harvested, the number of positive lymph nodes, and clinical stage. To account for changes in trends of clinical practice that occurred during the study period, the variable of the year of diagnosis was categorized into two distinct groups, including 2006 to 2009 and 2010 to 2016. These groups were selected because of the increased nationwide utilization of NAT in 2010 within the database. Treatment-related variables included type of NAT (TNT vs. CRT), time from diagnosis to neoadjuvant chemoradiation, and time from diagnosis to systemic chemotherapy. The NCDB does not provide information on specific comorbidities or chemotherapy regimens administered. In addition, it does not provide recurrence or disease specific survival.

Primary Outcome

For the purpose of comparison, patients were further categorized into 6 different groups according to their pathology results: ypT0N+, ypT0N0, ypT1-2N0, ypT3-4N0, ypT1-2N+, and ypT3-4N+. The primary outcome measured was the 5-year OS for all pathologic categories with particular focus on ypT0N+ as a comparison group.

Statistical Analysis

Descriptive statistics were utilized for patient characteristics. For continuous data, the mean and standard deviation (SD) were used to report normally distributed data and a comparison of each of the five other categories with ypT0N+ made by two-sample t-test. Median and interquartile range

(IQR) were used for non-normally distributed continuous data and a comparison of each group with ypT0N+ was made using the Mann–Whitney U test. For categorical data, results were summarized using counts (n) and percentages (%) while comparisons were made using Pearson's Chi-square test.

Survival was assessed on the basis of time from diagnosis to time of death or censoring. The Kaplan-Meier method was used to illustrate and compare the 5-year OS for the 6 groups with the log-rank test. To account for the possibility that survival outcomes of patients who received TNT vs. neoadjuvant CRT may differ, the results within each NAT modality were reported separately for each group. This was followed by running univariable and multivariable Cox proportional hazard regression to analyze OS with adjustment of other covariates, including age, gender, race, Charlson-Deyo score, clinical stage, year of diagnosis, number of lymph nodes positive and removed, surgical margins, grade, type of NAT, and time from diagnosis to neoadjuvant chemoradiation or systemic chemotherapy. Results of the multivariable adjusted Cox analysis were reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values. A complete case analysis approach was used to handle missing data. All statistical analyses were performed using Stata software version 16.0 (StataCorp, College Station, Texas, United States).

Results

A total of 32,843 patients with rectal adenocarcinoma were included, of whom 374 patients were ypT0N+ (table 1). There was a greater proportion of males across all pathologic categories ranging from 59.9% in ypT0N+ to 63.8% in ypT1-2N0. Median lymph nodes removed [IQR] ranged from 13 [9, 18] in ypT0N0 to 15 [12, 20] in ypT1-2N+ and ypT3-4N+. The median positive lymph nodes for ypT0N+ was 1 [1, 3].

Among ypT0N+ patients, 207 (55.3%) had moderately differentiated tumors and 45 (12.0%) had poorly differentiated tumors. In addition, 246 (65.7%) patients with ypT0N+ had their disease in the third clinical stage and 96 (25.7%) had their disease in the second clinical stage. The proportion of patients who received TNT ranged from 52.2% in ypT1-2N+ to 67.1% in ypT0N0. TNT was administered to 197 (52.7%) patients with ypT0N+ disease. Patients with ypT0N+ had a lower likelihood of receiving TNT than patients with node-negative categories.

Among patients who received TNT, developing ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0 (70.8% vs. 87.0% and 83.5%, respectively; $p<0.05$) (figure 2a). However, it was associated with a higher 5-year OS than ypT3-4N+ (70.8% vs. 51.6%; $p<0.05$) (table 2). There were no differences in 5-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+.

Similar results were found among patients who received neoadjuvant CRT and adjuvant chemotherapy. Achieving ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0 (82.5% vs. 94.9% and 91.3%, respectively; $p<0.05$) (figure 2b). However, ypT0N+ disease was associated with a better 5-year OS than ypT3-4N+ disease (82.5% vs. 61.2%; $p<0.05$). There

were no differences in 5-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+ among patients who received neoadjuvant CRT and adjuvant chemotherapy.

On the multivariable Cox regression, developing ypT0N0 and ypT1-2N0 was associated with 53.0% and 43.0% decreases in the hazard rate of death (HR=0.47, 95% CI: 0.36-0.63; p<0.001 and HR=0.57, 95% CI: 0.44-0.75; p<0.001, respectively) compared with ypT0N+ (table 3). On the other hand, having ypT3-4N+ disease was associated with a 62.0% increase in the hazard rate of death (HR=1.62, 95% CI: 1.24-2.10; p<0.001).

On the multivariable analysis of ypT0N+ patients (table 4), factors associated with a decrease in the OS included age (HR=1.05, 95% CI: 1.02-1.07; p<0.001), male gender (HR=2.01, 95% CI: 1.10-3.68; p=0.024), Charlson-Deyo score of ≥ 2 (HR=3.48, 95% CI: 1.18-10.30; p=0.024), and the presence of ≥4 positive lymph nodes (HR=2.37, 95% CI: 1.10-5.10; p=0.027). There was no difference in the OS between ypT0N+ patients who received TNT vs. neoadjuvant CRT and adjuvant chemotherapy.

Discussion

There is a void in categorizing and describing survival outcomes of ypT0N+ patients. The results of this study show that for patients diagnosed with rectal adenocarcinoma who undergo NAT (TNT or CRT) followed by surgical resection, achieving ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0. However, it was associated with improved 5-year OS compared with ypT3-4N+. There were no differences in 5-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+. Age, male gender, Charlson-Deyo score of ≥ 2, and having ≥4 positive lymph nodes were all associated with a decrease in the OS of ypT0N+ patients.

The role of the pathologic response after NAT in rectal cancer patients has been thoroughly examined in the medical literature.[7, 10] However, rare studies have examined survival of patients with ypT0N+ disease.[13-15] Our findings from this national study may be helpful in describing the 5-year OS of ypT0N+ as well as identification of factors associated with OS among those patients, given the category remains relatively unaccounted for in most staging systems.

In keeping with findings from this study, a previous study that used the Swedish Colorectal Cancer Registry showed that having ypT0N0 was associated with a 64.0% increase in the OS compared with ypT0N+ (HR= 0.36, 95% CI: 0.15- 0.86).[14] This was also reported in a retrospective analysis of factors influencing outcomes in rectal cancer patients treated with NAT in Korea, where the authors found that the 5-year OS was 91.3% for ypT0N0 compared with 62.5% for ypT0N1-2.[13] In a separate Italian Society of Surgical Oncology Young Board (YSICO) study, Lorenzon and colleagues reported that mortality of ypT0N+ patients was 4.48 times greater than ypT0N0 patients.[15] Finally, in the Korean Radiation Oncology Group study, having a positive nodal status

in ypT0 patients was associated with a decreased disease-free survival and OS compared with complete responders.[16] These findings are all uniformly consistent with findings in our NCDB analysis from the United States. In addition, our study provided a more detailed characterization of how survival outcomes of ypT0N+ compared not only with ypT0N0 but also with other pathologic categories. This may facilitate the inclusion of ypT0N+ in future iterations of the ypTNM staging system for rectal cancer. Moreover, our study may be helpful for physicians to counsel their rectal cancer patients on the possibility of having residual nodal involvement after complete tumor response following NAT and inform patients' regarding survival.

In our study, we found that the number of positive lymph nodes is an important prognostic determinant factor associated with a lower OS in ypT0N+ patients. This may be clinically significant while counselling patients about predictors of OS. In keeping with our findings, Lorenzon and colleagues reported nodal positivity as a prognostic factor that was correlated with a lower OS for ypT0N+ patients.[15] On the other hand, Lu and colleagues described the survival of 59 rectal cancer patients in China and compared the patients who had ypN+ with those who had ypN0. Strikingly, the authors found in their analysis that patients with ypN+ demonstrated higher OS than patients with ypN0 (90.9% vs. 70.0%; P=0.03).[17] However, the authors showed that ypN+ status was an independent risk factor associated with local recurrence[17], which was also shown by Jang and colleagues in their study.[13] It is difficult to reconcile this particular finding given that nodal positivity has largely been shown to adversely impact oncologic outcomes in patients with rectal cancer.

Locally advanced rectal cancer has traditionally been treated with neoadjuvant CRT followed by total mesorectal excision and adjuvant chemotherapy.[3] However, because of the adverse events associated with the adjuvant chemotherapy following major surgical intervention and potential associated complications, there has been an emerging switch to administer the entire course of systemic chemotherapy upfront in the form of TNT.[4] Although ypT0N+ was not included, another NCDB-based analysis (n= 9066) by Sutera and colleagues showed no differences in the OS, 30-day post-operative mortality, readmissions, or hospital length of stay between surgical patients who received TNT vs. CRT in the neoadjuvant setting.[4] This is in keeping with findings from our study showing no difference in OS among ypT0N+ patients who received TNT vs. neoadjuvant CRT and adjuvant chemotherapy.

This study has some limitations. First, the NCDB does not provide data on disease-specific survival or recurrence, which could be of special interest for ypT0N+ patients. Second, there was a lack of variables describing the different chemotherapy and radiation regimens that were used. Third, the detection of some statistical differences and the generalizability of the study may have been limited by the relatively small number of ypT0N+ patients. Finally, the results of this study should be interpreted considering the retrospective nature of the study, which may lead to residual confounding.

Conclusion

In patients with rectal adenocarcinoma who had NAT (either TNT or CRT) followed by surgical resection, achieving ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0. On the other hand, ypT0N+ disease was associated with improved 5-year OS compared with ypT3-4N+ disease. There were no differences in 5-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+. Age, male gender, Charlson-Deyo score of ≥2, and having ≥4 positive lymph nodes were all associated with a decrease in the OS of ypT0N+ patients.

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FIGURES AND TABLES

Figure (1): Overview of the selection criteria for the study cohort.

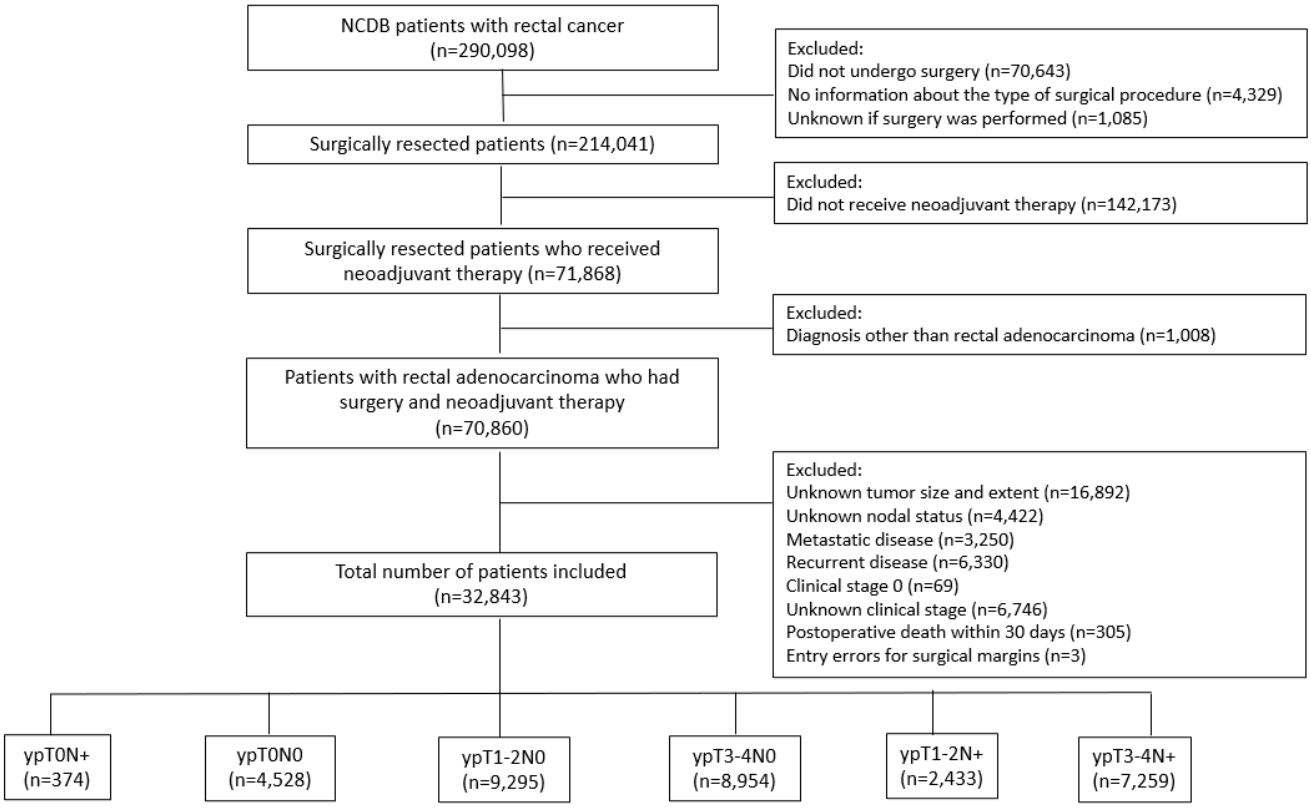


Figure (2a): 5-year overall survival of rectal cancer patients who received total neoadjuvant therapy.

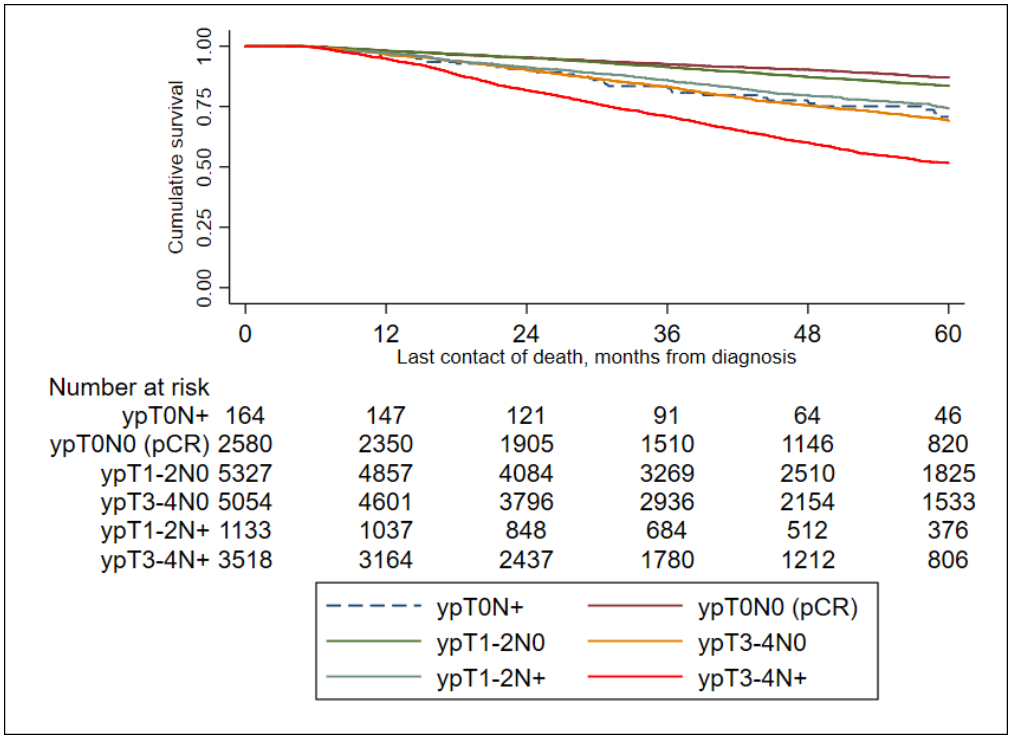
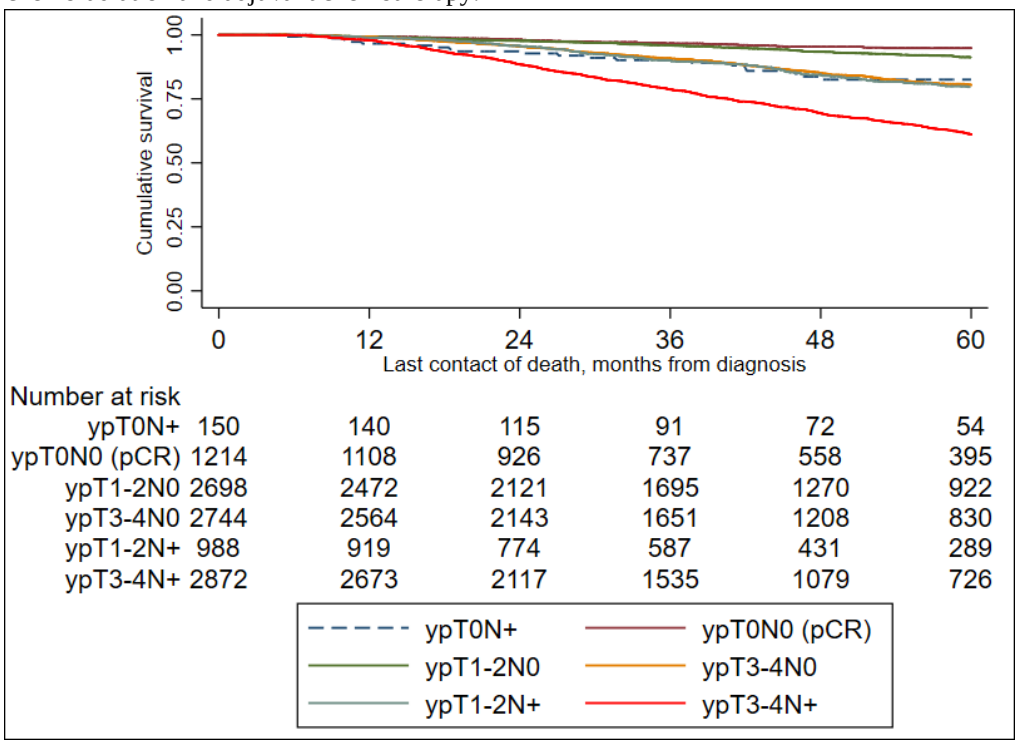


Figure (2b): 5-year overall survival of rectal cancer patients who received neoadjuvant chemoradiation and adjuvant chemotherapy.



pCR= pathologic complete response.

Table 1: Characteristics of rectal cancer patients.

Characteristic	ypT0N+ (n=374)	ypT0N0 (pCR) (n=4528)	ypT1-2N0 (n=9295)	ypT3-4N0 (n=8954)	ypT1-2N+ (n=2433)	ypT3-4N+ (n=7259)
Mean age± SD	58.5± 12.1	59.0± 11.8	59.5± 11.7	59.7± 11.9	56.6± 11.9*	57.2± 12.3*
Male gender, n (%)	224 (59.9)	2770 (61.2)	5933 (63.8)	5626 (62.8)	1468 (60.3)	4600 (63.3)
White race, n (%)	313 (83.7)	3923 (86.6)	8106 (87.2)*	7651 (85.4)	2087 (85.8)	6129 (84.3)
Year of diagnosis, n (%)		*				
2006-2009	57 (15.2)	521 (11.5)	1532 (16.5)	1572 (17.6)	394 (16.2)	1326 (18.3)
2010-2016	317 (84.8)	4007 (88.5)	7763 (83.5)	7382 (82.4)	2039 (83.8)	5933 (81.7)
Charlson-Deyo score, n (%)		*	*	*	*	
0	323 (86.4)	3587 (79.2)	7250 (78.0)	7076 (79.0)	1911 (78.5)	5907 (81.4)
1	41 (10.9)	714 (15.8)	1559 (16.8)	1459 (16.3)	416 (17.1)	1079 (14.9)
≥ 2	10 (2.7)	227 (5.0)	486 (5.2)	419 (4.7)	106 (4.4)	273 (3.7)
Clinical stage, n (%)		*	*	*	*	*
I	32 (8.6)	294 (6.5)	1096 (11.8)	327 (3.7)	134 (5.5)	209 (2.9)
II	96 (25.7)	1985 (43.8)	4115 (44.3)	4402 (49.2)	699 (28.7)	2069 (28.5)
III	246 (65.7)	2249 (49.7)	4084 (43.9)	4225 (47.1)	1600 (65.8)	4981 (68.6)
Median lymph nodes harvested [IQR]	14 [10, 18]	13 [9, 18]*	14 [10, 18]	14 [10, 19]	15 [12, 20]*	15 [12, 20]*
Median positive lymph nodes [IQR]	1 [1, 3]	0*	0*	0*	2 [1, 3]*	2 [1, 5]*
Number of positive lymph nodes, n (%)[a]		*	*	*	*	*
N0 (no regional lymph node metastasis)	0	4528 (100.0)	9295 (100.0)	8954 (100.0)	0	0
N1 (one to three regional lymph nodes are positive)	328 (87.7)	0	0	0	1975 (81.2)	4651 (64.1)
N2 (four or more regional lymph nodes are positive)	46 (12.3)	0	0	0	458 (18.8)	2608 (35.9)
Grade, n (%)		*	*	*	*	*
Well-differentiated	19 (5.1)	298 (6.6)	833 (9.0)	610 (6.8)	172 (7.1)	472 (6.5)
Moderately differentiated	207 (55.3)	2268 (61.1)	6671 (71.8)	6276 (70.1)	1728 (71.0)	4692 (64.6)
Poorly differentiated	45 (12.0)	271 (6.0)	655 (7.0)	931 (10.4)	276 (11.3)	1314 (18.1)
Unknown	103 (27.6)	1191 (26.3)	1136 (12.2)	1137 (12.7)	257 (10.6)	781 (10.8)
Surgical margins, n (%)			*	*	*	*
Negative	374 (100.0)	4497 (99.3)	9041 (97.3)	8187 (91.4)	2335 (96.0)	6258 (86.2)
Positive	0	0	85 (0.9)	416 (4.6)	36 (1.5)	530 (7.3)
Unknown	0	31 (0.7)	169 (1.8)	351 (4.0)	62 (2.5)	471 (6.5)
Type of neoadjuvant therapy, n (%)		*	*	*		
Total neoadjuvant therapy	197 (52.7)	3039 (67.1)	6079 (65.6)	5736 (64.1)	1271 (52.2)	3938 (54.2)
Neoadjuvant chemoradiation plus adjuvant chemotherapy	177 (47.3)	1489 (32.9)	3198 (34.4)	3218 (35.9)	1162 (47.8)	3321 (45.8)
Median time (days) from diagnosis to chemoradiation [IQR]	35 [25, 48]	36 [27, 49]	34 [25, 47]	34 [24, 47]	34 [25, 47]	33 [24, 46]
Median time (days) from diagnosis to systemic chemotherapy [IQR]	33 [23, 45]	34 [25, 48]	33 [24, 46]	33 [22, 46]	33 [24, 46]	32 [22, 45]

n= number of patients, SD= standard deviation, pCR= pathologic complete response.

*The p-value is less than 0.05 in reference to ypT0N+ category.

[a]Based on the American Joint Committee on Cancer (AJCC) categorization.

Table (2): 5-year overall survival of rectal cancer patients according to pathologic category.

Pathologic category	**Total neoadjuvant therapy**	**Chemoradiation *plus* adjuvant chemotherapy**
ypT0N0 (pCR)	87.0*	94.9*
ypT1-2N0	83.5*	91.3*
ypT0N+	70.8	82.5
ypT3-4N0	69.2	80.5
ypT1-2N+	74.2	79.7
ypT3-4N+	51.6*	61.2*

*Log-rank test p-value is less than 0.05 in reference to ypT0N+ category.
pCR= pathologic complete response.

Table (3): univariable and multivariable analysis of patient characteristics and their association with overall survival.

Variable	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.03	1.02- 1.04	<0.001	1.03	1.02- 1.04	<0.001
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.23	1.16- 1.29	<0.001	1.22	1.15- 1.29	<0.001
Race						
Non-white	Ref	Ref	Ref	Ref	Ref	Ref
White	0.91	0.85- 0.98	0.012	0.89	0.82- 0.95	0.001
Year of diagnosis						
2006-2009	Ref	Ref	Ref	Ref	Ref	Ref
2010-2016	0.99	0.93- 1.05	0.67	1.10	1.03- 1.17	0.002
Pathologic category						
ypT0N+	Ref	Ref	Ref	Ref	Ref	Ref
ypT0N0 (pCR)	0.49	0.37- 0.64	<0.001	0.47	0.36- 0.63	<0.001
ypT1-2N0	0.62	0.48- 0.80	<0.001	0.57	0.44- 0.75	<0.001
ypT3-4N0	1.19	0.93- 1.54	0.17	1.09	0.84- 1.43	0.51
ypT1-2N+	1.02	0.78- 1.33	0.90	0.88	0.67- 1.17	0.38
ypT3-4N+	2.14	1.66- 2.76	<0.001	1.62	1.24- 2.10	<0.001
Charlson-Deyo score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.46	1.38- 1.56	<0.001	1.33	1.25- 1.42	<0.001
≥ 2	2.08	1.88- 2.30	<0.001	1.87	1.68- 2.07	<0.001
Clinical stage						
I	Ref	Ref	Ref	Ref	Ref	Ref
II	1.18	1.06- 1.31	0.002	1.02	0.91- 1.14	0.72
III	1.22	1.10- 1.35	<0.001	0.97	0.87- 1.08	0.56
Number of lymph nodes harvested	0.99	0.989-0.995	<0.001	0.99	0.985- 0.991	<0.001
Number of positive lymph nodes	1.10	1.09- 1.11	<0.001	1.07	1.06- 1.08	<0.001
Grade						
Well-differentiated	Ref	Ref	Ref	Ref	Ref	Ref
Moderately differentiated	1.03	0.93- 1.15	0.52	1.01	0.91- 1.12	0.86
Poorly differentiated	1.90	1.69- 2.12	<0.001	1.47	1.31- 1.66	<0.001
Surgical margins						
Negative	Ref	Ref	Ref	Ref	Ref	Ref

Positive	3.05	2.77- 3.37	<0.001	2.10	1.90- 2.32	<0.001
Type of neoadjuvant therapy, n (%)						
Total neoadjuvant therapy	Ref	Ref	Ref	Ref	Ref	Ref
Neoadjuvant chemoradiation plus adjuvant chemotherapy	0.71	0.68- 0.75	<0.001	0.69	0.65- 0.73	<0.001
Days from diagnosis to chemoradiation	1.00	0.99- 1.01	0.06	1.00	0.99- 1.01	0.97
Days from diagnosis to systemic chemotherapy	1.00	0.99- 1.00	0.20	1.00	0.99- 1.00	0.37

HR= hazard ratio, CI= confidence interval, pCR= pathologic complete response.

Table (4): Subgroup analysis of ypT0N+ patients' characteristics and their association with overall survival.

Variable	Univariable			Multivariable		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.05	1.03- 1.07	<0.001	1.05	1.02- 1.07	<0.001
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.71	0.98- 3.00	0.06	2.01	1.10- 3.68	0.024
Race						
Non-white	Ref	Ref	Ref	Ref	Ref	Ref
White	1.52	0.72- 3.20	0.27	1.14	0.52- 2.48	0.75
Year of diagnosis						
2006-2009	Ref	Ref	Ref	Ref	Ref	Ref
2010-2016	1.30	0.69- 2.44	0.41	1.59	0.79- 3.21	0.20
Charlson-Deyo score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.72	0.84- 3.52	0.14	1.85	0.82- 4.17	0.14
≥ 2	5.75	2.05- 16.12	0.001	3.48	1.18- 10.30	0.024
Clinical stage						
I	Ref	Ref	Ref	Ref	Ref	Ref
II	0.94	0.41- 2.14	0.88	0.84	0.33- 2.16	0.72
III	0.66	0.30- 1.43	0.29	0.70	0.29- 1.70	0.43
Number of lymph nodes harvested	0.98	0.95- 1.01	0.17	0.97	0.94- 1.01	0.18
Number of positive lymph nodes[a]						
N1 (one to three regional lymph nodes are positive)	Ref	Ref	Ref	Ref	Ref	Ref
N2 (four or more regional nodes are positive)	1.87	0.97- 3.60	0.06	2.37	1.10- 5.10	0.027
Grade						
Well-differentiated	Ref	Ref	Ref	Ref	Ref	Ref
Moderately differentiated	0.51	0.18- 1.47	0.22	0.43	0.13- 1.37	0.15
Poorly differentiated	0.82	0.25- 2.67	0.74	0.58	0.16- 2.14	0.42
Type of treatment received, n (%)						
Total neoadjuvant therapy	Ref	Ref	Ref	Ref	Ref	Ref
Neoadjuvant chemoradiation plus adjuvant chemotherapy	0.69	0.41- 1.15	0.16	0.63	0.36- 1.10	0.11
Days from diagnosis to chemoradiation	0.99	0.98- 1.01	0.41	1.00	0.98- 1.02	0.82
Days from diagnosis to systemic chemotherapy	1.00	0.98- 1.01	0.43	0.99	0.97- 1.01	0.29

[a]Based on the American Joint Committee on Cancer (AJCC) categorization.

HR= hazard ratio, CI= confidence interval

SUPPLEMENTARY MATERIALS

Supplementary table (1): Comparison of the characteristics of the included vs. excluded patients.

Characteristic	Included patients (n=32843)	Excluded Patients (n=239554)	p-value
Mean age± SD	58.7± 11.9	64.2± 13.7	<0.001
Male gender, n (%)	20614 (62.8)	137536 (57.4)	<0.001
White race, n (%)	28203 (85.9)	200057 (83.5)	<0.001
Year of diagnosis, n (%)			
2006-2009	5402 (16.4)	108995 (45.5)	<0.001
2010-2016	27441 (83.6)	130559 (54.5)	
Charlson-Deyo score, n (%)			
0	26054 (79.3)	183663 (76.7)	<0.001
1	5268 (16.0)	40462 (16.9)	
≥ 2	1521 (4.7)	15429 (6.4)	
Clinical stage, n (%)			
I	2092 (6.4)	46679 (19.5)	<0.001
II	13366 (40.7)	33808 (14.1)	
III	17385 (52.9)	33767 (14.1)	
Median lymph nodes harvested [IQR]	14 [11, 19]	1 [0, 15]	<0.001
Median positive lymph nodes [IQR]	0 [0, 1]	0 [0, 1]	<0.001
Number of positive lymph nodes, n (%)[a]			
N0 (no regional lymph node metastasis)	22777 (69.4)	74842 (31.2)	<0.001
N1 (one to three regional lymph nodes are positive)	6954 (21.1)	24832 (10.4)	
N2 (four or more regional lymph nodes are positive)	3112 (9.5)	139880 (58.4)	
Grade, n (%)			
Well-differentiated	2404 (7.4)	25619 (10.7)	<0.001
Moderately differentiated	22342 (68.0)	126111 (52.6)	
Poorly differentiated	3492 (10.6)	27787 (11.6)	
Unknown	4605 (14.0)	60037 (25.1)	
Surgical margins, n (%)			
Negative	30692 (93.5)	210447 (87.8)	<0.001
Positive	1067 (3.2)	8417 (3.5)	
Unknown	1084 (3.3)	20690 (8.7)	
Type of neoadjuvant therapy, n (%)			
Total neoadjuvant therapy	20278 (61.7)	28292 (11.8)	<0.001
Neoadjuvant chemoradiation plus adjuvant chemotherapy	12565 (38.3)	10937 (3.5)	
Median time (days) from diagnosis to chemoradiation [IQR]	34 [25, 47]	41 [26, 69]	<0.001
Median time (days) from diagnosis to systemic chemotherapy [IQR]	33 [23, 46]	39 [25, 62]	<0.001

n= number of patients, SD= standard deviation, pCR= pathologic complete response.

[a]Based on the American Joint Committee on Cancer (AJCC) categorization.

SUMMARY OF PAPERS

Paper 1

We conducted a survival analysis using the National Cancer Database (NCDB) to describe the survival outcomes of patients with gastric adenocarcinoma who had neoadjuvant therapy followed by surgery between 2004 and 2016. Patients were categorized into six pathologic groups: (i) ypT0N+ (ii) ypT0N0 (iii) ypT1-2N0 (iv) ypT3-4N0 (v) ypT1-2N+ (vi) ypT3-4N+. The primary outcome measured was 5-year overall survival (OS) and secondary outcomes included 3-year and 1-year OS for each category.

Achieving ypT0N+ was associated with a lower 5-year and 3-year OS than ypT0N0 and ypT1-2N0. There were no differences in 1-year OS between ypT0N+ and ypT0N0 or ypT1-2N0. There were also no differences in 5-year, 3-year, or 1-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+. On the other hand, ypT0N+ disease was associated with improved 5-year OS compared with ypT3-4N+. However, there were no differences in 3-year or 1-year OS between ypT0N+ and ypT3-4N+.

Paper 2

We conducted a survival analysis using the NCDB to describe the 5-year OS of patients with rectal adenocarcinoma who had neoadjuvant therapy followed by surgery between 2006 and 2016. Patients were categorized into six pathologic groups: (i) ypT0N+ (ii) ypT0N0 (iii) ypT1-2N0 (iv) ypT3-4N0 (v) ypT1-2N+ (vi) ypT3-4N+. The primary outcome measured was 5-year OS of each category with a particular focus on that of ypT0N+.

Developing ypT0N+ was associated with a lower 5-year OS than ypT0N0 and ypT1-2N0. On the other hand, ypT0N+ disease was associated with improved 5-year OS compared with ypT3-4N+ disease. There were no differences in 5-year OS between ypT0N+ and ypT3-4N0 or ypT1-2N+.

DISCUSSION AND PERSPECTIVES

There has been a growing interest in the use of neoadjuvant therapy as a component of the multimodal treatment for patients with gastric or rectal cancers.[4,10] This shift in the treatment paradigm has required the American Joint Committee on Cancer (AJCC) to create a ypTNM staging system to inform physicians about the survival outcomes of gastric cancer patients who underwent neoadjuvant therapy followed by surgical resection. However, this staging system does not include both ypT0N0 and ypT0N+.[6] Importantly, there is still a substantial need to establish a similar ypTNM staging for rectal cancer patients who had neoadjuvant therapy and surgery.

The pathologic complete response (ypT0N0) has been investigated thoroughly in the literature.[8,11,12] On the other hand, survival outcomes of patients with ypT0N+ are poorly described. We hope that our studies can facilitate the inclusion of ypT0N+ in the future iterations of the AJCC ypTNM staging systems.

We also think that our results may be clinically meaningful for patient counselling. It is important to educate patients with gastric or rectal adenocarcinoma about their possibility of exhibiting a complete response in the primary tissue with residual tumor seen only in the adjacent lymph nodes after undergoing neoadjuvant therapy and surgery. Our results may also be helpful to enlighten ypT0N+ patients about their survival outcomes and predictors of survival.

Lastly, we believe that our studies may open further perspectives for future randomized controlled trials to compare the effect of the different neoadjuvant therapies on the survival outcomes of ypT0N+ patients. In addition, building and validating prediction models for the survival of ypT0N+ patients may also be of special interest to this unique group of patients.

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