Original Article

ypT0 gastric carcinoma after preoperative chemotherapy: a unique status according to AJCC 8th edition cancer staging system

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Background: American Joint Committee on Cancer (AJCC) recently had published 8th edition staging system, in which a separate staging system was proposed for gastric cancers those received preoperative therapy (ypStage), however ypT0 was not included. The aim of this study was to propose the inclusion of ypT0 into the new staging classification.

Methods: We collected data of gastric cancer patients who underwent gastrectomy after preoperative chemotherapy in the First Affiliated Hospital of Zhejiang University (2004–2015). Kaplan-Meier survival estimations and log-rank tests were performed to compare survival.

Results: 314 patients were enrolled in this study according to inclusion and exclusion criteria. The 5-year overall survival (OS) rate of all patients was 53.5% and the survival estimation was well discriminated by ypstage (P<0.001). Twenty-five patients were identified achieving pathological complete regression in primary lesion (ypT0), in which there were 16 pCR patients and 9 ypT0N+ patients. The 5-year OS of pCR patients was 93.8%, which was not better than ypstage I with 5-year OS of 97.5% (P=0.507). Meanwhile, ypT0N+ patients' 5-year OS was 66.7%, which was significantly shorter than those with ypstage I (P=0.002), but no statistical difference from ypstage II with 5-year OS of 71.6% (P=0.583).

Conclusions: Complete pathological regression of primary lesion (ypT0) was a predictor for long-term outcomes. pCR and ypT0N+ patients might be considered for inclusion in the ypstage I and ypstage II group respectively.

Keywords: Preoperative chemotherapy; stomach neoplasms; TNM staging

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Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer related deaths worldwide (1). Majority of gastric cancer patients are diagnosed at advanced stage. The prognosis of advanced gastric cancer is poor and multimodal strategy is necessary to improve the survival. Perioperative chemotherapy is an optional treatment strategy for advanced gastric cancer.

The tumor-node-metastasis (TNM) classification proposed by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) is a globally used standard to stage most malignancies, including gastric cancer. Recently, AJCC released the eighth edition of TNM staging system (2). One of the most notable updates in gastric cancer section was that new edition has three discrete staging system: pre-treatment clinical stage of the disease (cTNM), the pathological stage after upfront surgery (pTNM) and the pathological stage after preoperative therapy (ypTNM). The reasonable of

creating novel ypstage was based on the assumption that the prognosis is different between patients with the same TNM stage who received preoperative therapy or not. Besides, ypstage represent the combinate of TNM status and the response to preoperative therapy.

ypT0 is defined as no evidence of tumor in primary lesion which is represent the best response to preoperative therapy. There are two conditions: one is ypT0 with no residual tumor in resected lymph nodes (ypT0N0), which is known as pathological complete response (pCR), the other is ypT0 with metastatic lymph nodes (ypT0N+). However, neither conditions were included in the 8th edition of staging system. Furthermore, there is still debate about whether pathological complete response after preoperative chemotherapy is related to the survival (3,4).

The aims of this retrospective study included (I) to evaluate the prognosis of ypT0 patients. (II) propose the inclusion of ypT0 patients into the TNM staging system as supplement. We present the following article in accordance with the STORBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2426).

Methods

Patients

We conducted a retrospective collection of gastric cancer patients who received preoperative chemotherapy in the First Affiliated Hospital of Zhejiang University from July 2004 to December 2015. The inclusion criteria included (I) histologically confirmed gastric adenocarcinoma by endoscopic biopsy before the treatment initiation; (II) the primary lesion invaded the serosa or had the involvement of adjacent structures with/without the lymph node metastasis ($cT_{4a/4b}N_{any}$), which was mainly evaluated by computed tomography (CT); (III) curative resection with D2 lymphadenectomy followed by chemotherapy; The exclusion criteria were as follows: (I) distant metastasis before the treatment or confirmed during the surgery; (II) massive gastrointestinal hemorrhage or gastric outlet obstruction.; (III) previous cytotoxic chemotherapy, radiotherapy, target therapy, or immunotherapy for any tumor; (IV) history of another malignancy, except cured basal cell carcinoma of the skin or cured carcinoma in situ of the uterine cervix, and (V) prior major stomach surgery.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2020IIT-92). Written informed consent form was obtained from all patients.

Preoperative chemotherapy

The regimens of preoperative chemotherapy included S-1 combined with oxaliplatin (SOX), Capecitabine combined with oxaliplatin (XELOX) and fluorouracil, leucovorin plus oxaliplatin (FOLFOX). SOX consisted of oxaliplatin 130 mg/m^2 as a 2-h intravenous infusion on day 1, and S-1 was given orally twice daily for 2 weeks followed by a 7-day rest period. The dose of S-1 was 80 mg/day for body surface area (BSA) <1.25 m^2, 100 mg/day for BSA ≥1.25 to <1.5 m^2, and 120 mg/day for BSA ≥1.5 m^2. XELOX consisted of oxaliplatin 130 mg/m^2 as a 2-h intravenous infusion on day 1, oral capecitabine of 1,000 mg/m^2 twice daily on days 1–14. FOLFOX consisted of oxaliplatin 130 mg/m^2 as a 2-h intravenous infusion on day 1, leucovorin 400 mg/m^2, and a bolus of 5-FU 400 mg/m^2 on day 1, followed by a 46-h infusion of 5-FU at 2,400 mg/m^2. All regimens were repeated every 3 weeks.

Surgery

Patients underwent curative resection in two weeks after the completion of the last cycle of preoperative chemotherapy. Distal or total gastrectomy or combined resection was performed, depending on the location and extent of the primary tumor. D2 lymphadenectomy was conducted by experienced surgeons according to the criteria established by Japanese Gastric Cancer Association (JGCA) (5). The reconstruction type was determined by surgeon's decision. Postoperative chemotherapy was continued within 4–6 weeks after surgery for patients with good physical status. The cycles and regimens were decided by the oncologist according to the response and adverse events. Yield pathological TNM (ypTNM) staging was evaluated according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Handbook (2).

Follow-up

After completion of the treatment, the patients were followed up every 3–6 months in the first two years, and 6–12 months from the third to the fifth years, and then annually thereafter. The follow-up included complete blood counts, chemistry profile, tumor markers, endoscopy, and

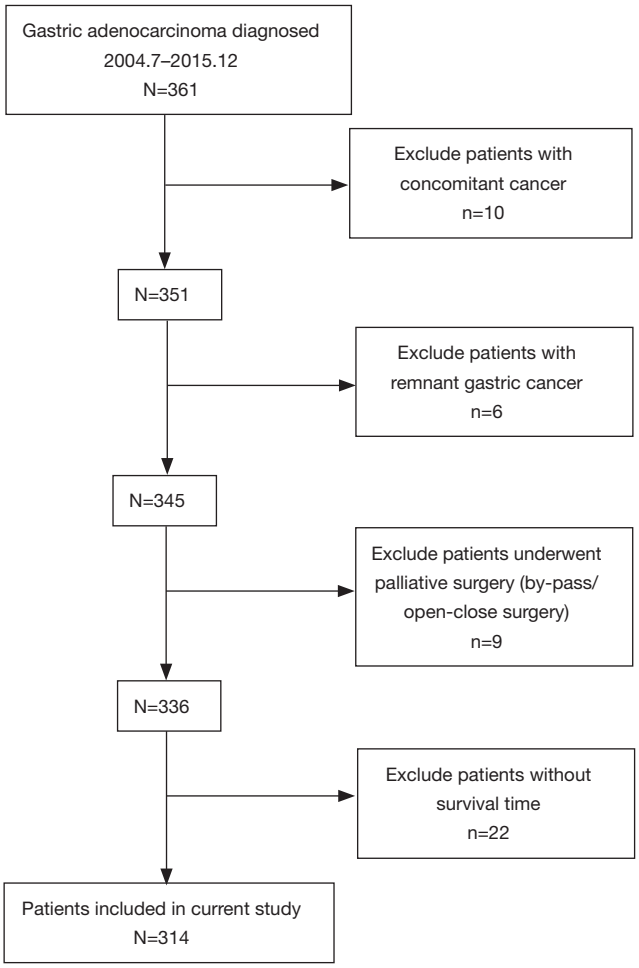

Figure 1 Flow-chart of patients' inclusion and exclusion process.

radiological imaging examinations.

Statistical analysis

Overall survival (OS) was calculated from the start of treatment to the date of death from any cause or the day of last follow-up. Kaplan Meier curves were compared using the log-rank test for OS. Hazard ratio (HR) and 95% confidential interval (CI) were calculated by Cox proportional-hazards regression models. The variables with P value less than 0.05 in univariate analysis were included into multivariate analysis. Multivariate survival analysis was performed using the likelihood ratio test of the Cox proportional hazards model. Categorical variables were conducted using the χ^2 test or Fisher's exact test if necessary. Mean ± SD or Median values were used to describe continuous data, and Students' *t*-test or the Mann-Whitney U-test was used to compare continuous variables. All statistical analysis was performed by IBM SPSS Statistics, Version 24.0 (IBM Corp., Armonk, NY, USA), and a two-tailed P<0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of all patients

A total of 361 gastric adenocarcinoma patients who received preoperative chemotherapy were identified from July 2004 to December 2015. Finally, 314 patients were enrolled in the study according to the inclusion and exclusion criteria. *Figure 1* showed patients' selection process. The baseline characteristics of all patients were summarized in *Table 1*. The median age was 62 years old (range 32–80). In enrolled patients, 230 patients were male, and 84 patients were female. The median cycle of preoperative chemotherapy was 3 (range 1–7). 297 patients (94.6%) received R0 resection. As to the pathological findings, the mean number of retrieved lymph nodes was 33.8±13.1 with the average positive lymph nodes of 4.9±6.7. There were 22 ypT1 patients (7%), 46 ypT2/3 patients (14.6%) and 221 ypT4 patients (70.4%). 212 patients (67.5%) had positive lymph nodes after preoperative chemotherapy, in which 67 patients were ypN1 (21.3%), 69 patients were ypN2 (22%) and 76 patients were ypN3 (24.2%) respectively. There were 40 ypstage I patients (12.7%), 68 ypstage II (21.7%) and 181 ypstage III patients (57.6%). There were 54 patients (17.2%) had surgical complications. 245 (78%) patients received postoperative chemotherapy, 43 (13.7%) patients didn't continue postoperative chemotherapy and the other 26 (8.3%) patients' postoperative treatment status was unknown.

Twenty-five patients (8%) were identified to have complete tumor regression in primary lesion (ypT0). All patients were divided into two groups (ypT0 and notypT0 group) according to whether complete pathological regression was achieved. The demographic and clinical characteristics of two groups were showed in *Table 1*. Preoperative regimen was significantly related to higher ypT0 rate (P<0.001). Total number of retrieved lymph nodes has no difference between patients with ypT0 and not ypT0 (P=0.531). The median number of retrieved lymph nodes was 31 (range 12–67) and 32 (range 9–86) for ypT0 and notypT0 respectively. In ypT0 group, the mean number of positive lymph nodes (1.0±1.8) was lower than that in

Table 1 Baseline characteristics of enrolled patients

	ypT0 (n=25)	notypT0 (n=289)	Total (N=314)	P
Age, yr				0.820
Median	62	62	62	
Range	45–77	32–80	32–80	
Gender, n (%)				
Male	17 (68.0)	213 (73.7)	230 (73.2)	0.537
Female	8 (32.0)	76 (26.3)	84 (26.8)	
cN, n (%)				0.318
cN (+)	21 (84.0)	217 (75.1)	238 (75.8)	
cN (-)	4 (16.0)	72 (24.9)	76 (24.2)	
ECOG status, n (%)				0.032
0	8 (32.0)	116 (40.1)	124 (39.5)	
1	10 (40.0)	143 (49.5)	153 (48.7)	
2	7 (28.0)	30 (10.4)	37 (11.8)	
Primary tumor location, n (%)				0.277
Upper	7 (28.0)	49 (17)	56 (17.8)	
Middle	4 (16.0)	47 (16.3)	51 (16.2)	
Lower	10 (40.0)	166 (57.4)	176 (56.1)	
MRI	4 (16.0)	27 (9.3)	31 (9.9)	
Regimen, n (%)				<0.001
FOLFOX	2 (8.0)	154 (53.3)	156 (49.7)	
XELOX	6 (24.0)	40 (13.8)	46 (14.6)	
SOX	17 (68.0)	95 (32.9)	112 (35.7)	
Preoperative cycles				0.383
Median	3	3	3	
Ranges	2–6	1–7	1–7	
Gastrectomy, n (%)				0.543
Distal gastrectomy	12 (48.0)	157 (54.3)	169 (53.8)	
Total gastrectomy	13 (52.0)	132 (45.7)	145 (46.2)	
Combined resection, n (%)				0.550
Yes	2 (8.0)	41 (14.2)	43 (13.7)	
No	23 (92.0)	248 (85.8)	271 (86.3)	
Residual tumor, n (%)				1.000
R0	24 (96.0)	273 (94.5)	297 (94.6)	
R1/2	1 (4.0)	16 (5.5)	17 (5.4)	

Table 1 (*continued*)

Table 1 (*continued*)

	ypT0 (n=25)	notypT0 (n=289)	Total (N=314)	P
Positive lymph nodes (mean ± SD)	1.0±1.8	4.9±6.7	4.6±6.5	0.004
Retrieved lymph nodes (mean ± SD)	32.2±15.1	34.0±13.0	33.8±13.1	0.531
ypN status, n (%)				<0.001
ypN (+)	9 (36.0)	203 (70.2)	212 (67.5)	
ypN (-)	16 (64.0)	86 (29.8)	102 (32.5)	
Postoperative complications, n (%)				0.164
Yes	7 (28.0)	47 (16.3)	54 (17.2)	
No	18 (72.0)	242 (83.7)	260 (82.8)	
Postoperative chemotherapy, n (%)				0.941
Yes	19 (76.0)	226 (78.2)	245 (78)	
No	4 (16.0)	39 (13.5)	43 (13.7)	
Unknown	2 (8.0)	24 (8.3)	26 (8.3)	

ECOG, Eastern Cooperative Oncology Group; MRI, multiple regions involved; FOLFOX, fluorouracil, leucovorin and oxaliplatin; XELOX, capecitabine and oxaliplatin; SOX, S-1 and oxaliplatin.

notypT0 group (4.9±6.7) (P=0.004), meanwhile there were less patients with metastatic nodes in ypT0 group (36% *vs.* 70.2%, P<0.001).

Follow-up and overall survival in all patients

All patients were followed up periodically until March 2020 and 165 patients (52.5%) had died at last time of follow-up. The median follow-up time was 55.5 months (range 7 to 169 months). The 5-year overall survival rate of all patients was 53.5% (*Figure 2A*). The overall survival estimation was well discriminated by ypstage. The 5-year overall survival rate of ypstage I, ypstage II and ypstage III were 97.5%, 71.6% and 32.7% respectively. The difference of overall survival by ypstage was statistically significant as the entire model (P<0.001). The differences of survival between ypstage I and II (P<0.001), and between ypstage II and III were also significant (P<0.001).

Five-year overall survival of ypT0, ypT1, ypT2/3 and ypT4 was 83.8%, 100%, 76% and 40.5% respectively, the difference was significant as the entire model (P<0.001). However, the difference in overall survival was marginally significant either between ypT0 and ypT2/3 (P=0.08) or between ypT0 and ypT1 patients (P=0.051). Overall survival could be well discriminated by ypN stage (P<0.001). The 5-year overall survival was 82.9%, 63.8%, 39.6% and 16% for ypN0, ypN1, ypN2 and ypN3 patients respectively. For adjacent ypN categories, the difference was also significant between ypN0 and ypN1 patients (P<0.001), ypN1 and ypN2 patients (P=0.011), and between ypN2 and ypN3 patients (P<0.001). Compared with ypT, ypN category showed better discrimination in overall survival estimation.

The 5-year overall survival of ypT0 patients was significantly better than those patients with residual tumor in primary lesion (83.8% *vs.* 50.9%, P=0.001) (*Figure 2B*). Results of univariable and multivariable analysis were summarized in *Table 2*. In univariate analysis, the preoperative regimen (P=0.001), preoperative cycles (P=0.04), concomitant resection (P=0.015), histological grade (P<0.001), residual tumor (P<0.001), ypT (P=0.002) and ypN (P<0.001) were significantly associated with overall survival. These variables were included into multivariate analysis. Multivariable analysis with COX forward regression for OS revealed that ypT0 was an independent predictor for long-term survival (P=0.025).

The characteristics and survival of pCR and ypT0N+

Twenty-five patients had pathological complete response in primary lesion, in which 9 patients were found had metastasis in dissected lymph nodes. The mean number of positive lymph nodes in ypT0 patients was 1±1.8. There

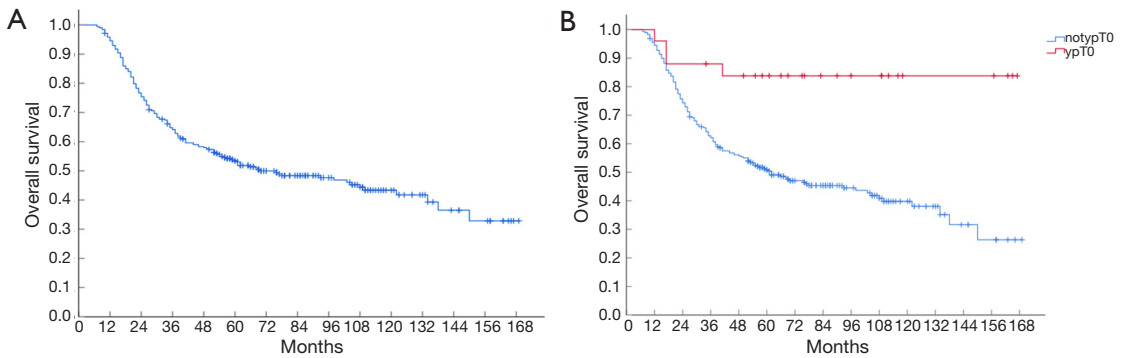

Figure 2 (A) Kaplan-Meier estimates for overall survival (OS) of all enrolled patients. (B) Kaplan-Meier estimates for OS according to whether residual tumor was observed in primary lesion or not (P=0.001).

Table 2 Univariable and multivariable analysis of overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Regimen		0.001		0.164
FOLFOX	ref			
XELOX	0.944 (0.621–1.436)	0.788		0.360
SOX	0.487 (0.335–0.707)	<0.001		0.062
Preoperative cycles		0.040		0.173
>4	Ref			
3-4	0.645 (0.399–1.042)	0.073		0.437
1-2	0.527 (0.321–0.866)	0.012		0.766
Concomitant resection		0.015		0.058
Yes	Ref			
No	0.604 (0.402–0.908)			
Histological grade		<0.001		0.356
Gx	ref			
Well differentiated	3.138 (1.170–8.414)	0.023		0.224
Poorly differentiated	5.271 (2.156–12.885)	<0.001		0.160
Residual tumor				
R0	ref		ref	
R1/2	3.401 (2.023–5.716)	<0.001	2.484 (1.477–4.178)	0.001
ypT				
ypT0	ref		ref	
notypT0	4.699 (1.738–12.701)	0.002	3.146 (1.157–8.551)	0.025
ypN				
ypN-	ref		ref	
ypN+	5.555 (3.401–9.074)	<0.001	4.919 (3.002–8.059)	<0.001

XELOX, capecitabine and oxaliplatin; SOX, S-1 and oxaliplatin; FOLFOX, fluorouracil, leucovorin and oxaliplatin; ref, reference; Gx, Grade cannot be assessed. Well differentiated: well and moderate differentiated. Poorly differentiated: undifferentiated and poorly differentiated.

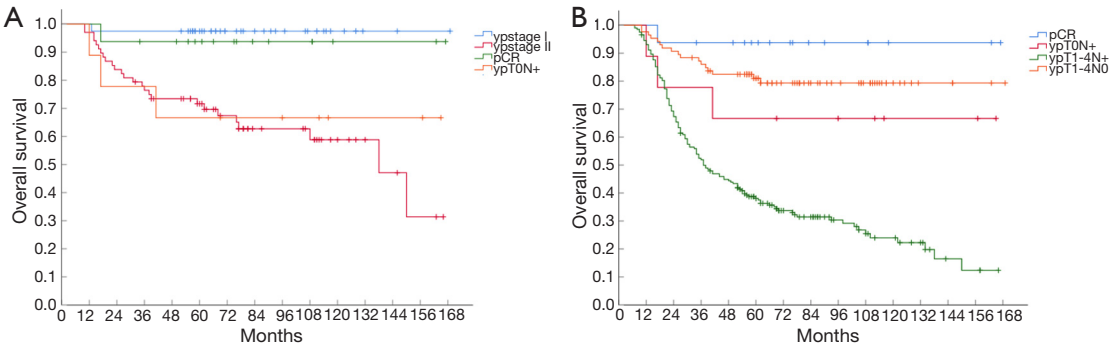

Figure 3 (A) Kaplan-Meier estimates for overall survival (OS) of patients with pCR, ypT0N+, ypstage I and II (P<0.001); (B) Kaplan–Meier estimates for OS according to whether residual tumor was observed in primary lesion (ypT0 and ypT1-4) and the lymph nodes status (N0 and N+) (P<0.001).

were 4 ypN1 patients, 4 ypN2 patients and 1 ypN3 patient respectively.

Four patients had died from cancer recurrence when the last follow-up (1 patient in pCR and 3 patients in ypT0N+). The first relapse sites included peritoneal spreading, locoregional lymph nodes, hepatic and anastomosis recurrence. The prognosis of ypT0 patients was between ypstage I and ypstage II. The difference was significant either between ypT0 and ypstage I (P=0.048) or ypstage II (P=0.043).

ypT0 patients were divided into two subgroups of pCR (n=16) and ypT0N+ (n=9) according to the status of ypN. The 5-year overall survival of pCR were 93.8% (*Figure 3A*). ypT0N+ patients had shorter 5-year overall survival of 66.7%, the difference was marginally significant compared with pCR (P=0.08). The overall survival has no difference between ypstage I and pCR (P=0.507). The prognosis of ypT0N+ patients was significantly worse than that of ypstage I patients (P=0.002), meanwhile, the difference of overall survival between ypT0N+ and ypstage II was not significant (P=0.583). The 5-year overall survival of ypT0N1 and ypT0N2 were both 75%, the survival time of ypT0N3 patient was 17 months. The difference was significant between ypT0N1 and ypstage I patients (P=0.029), ypT0N2 and ypstage I patients (P=0.046), and marginally significant between ypT0N1 and ypstage III patients (P=0.075), ypT0N2 and ypstage III patients (P=0.075). However, the different was not significant between ypT0N1 and ypstage II patients (P=0.371), ypT0N2 and ypstage II patients (P=0.601).

There were 4 patients with cN (-) and 21 patients with cN (+) in ypT0 group. The 5-year overall survival was for 80.7% cN (+) and for 100% cN (-), the difference was not significant (P=0.358).

Patients with residual tumor were also divided into two groups according to the lymph nodes status that ypT1-4N+ (n=203) and ypT1-4N0 (n=86). Compared with patients with ypT0, ypT1-4N+ patients showed worst long-term outcome with 5-year overall survival of 38.1% (*Figure 3B*). Patients with residual tumor but negative lymph nodes (ypT1-4N0) had 5-year OS of 81%, which was better than those with ypT0N+ (66.7%), but the difference was not statistically significant (P=0.339).

Discussion

In this retrospective study, we analyzed the pathological data and long-term outcome of gastric cancer patients after preoperative chemotherapy followed by curative surgery. The results showed that AJCC 8th edition staging system effectively predicted the survival. However, the results suggested that the long-term outcome of pCR patients was not better than that of ypstage I (P=0.507), and ypT0N+ patients had shorter survival than ypstage I (P=0.002), but similar with ypstage II (P=0.583).

Several large-scale randomized trials had demonstrated that perioperative chemotherapy could improve the prognosis of locally advanced gastric or gastroesophageal adenocarcinoma patients (6,7). The 8th TNM staging system was released by AJCC recently, in which the staging after preoperative therapy (ypstage) was described for the first time. Limited studies were conducted to evaluate the predictive value of new edition staging system (8). In current study, we found the overall survival could be

stratified by the new edition ypstage categories. ypT0 represented the best response to preoperative therapy, however, new edition of TNM stage of gastric cancer didn't address these patients. In our study, 25 patients were found no residual tumors in primary lesion (ypT0) and 16 patients achieved pCR (5.1%), which was comparable to previous studies (3,8,9). Pathological complete response was a predictor of better prognosis in several kinds of cancers after neoadjuvant chemotherapy (10-12). Most studies about prognosis after neoadjuvant chemotherapy focused on the comparison of overall survival between responder and non-responder, few studies investigated the long-term outcome of patients with pCR (13,14). Our study also showed the best overall survival in gastric cancer patients with pCR, which was supported by recent meta-analysis (15). We found that the long-term outcomes of pCR patients were no better than ypstage I patients, which was similar to previous study (8). The probable reasons for this condition were as follows: (I) ypstage I was related to good response to neoadjuvant chemotherapy, which resulted the 5-year overall survival of 97.5%. (II) Despite patients with pCR were likely to be cured, they still have chances of recurrence even after radical resection (15). As the limited cases and events of both conditions, it's hard to analyze the risk factors for recurrence and address the significant difference between pCR and ypstage I. Despite the favorable long-term outcome of patients with pCR, our result showed that the prognosis of ypT0 was intermediate. We thought it might be because the affection of patients with ypT0N+.

ypT0N+ was a unique condition that complete pathological regression in primary lesion but persist metastatic lymph nodes. Given the rarity of such situation, few studies had been reported in gastric cancer. In current study, we found that the prognosis of ypT0N+ patients was worse than those with pCR despite the difference was not statistically different (5-year OS: 66.7% *vs.* 93.7%, P=0.08). It might be due to the small population and low rate of events in both conditions. Besides, the overall survival of ypT0N+ disease was significantly worse than ypstage I, but similar with ypstage II. Min P and collogues analyzed ypT0N+ patients with esophagus cancer after chemotherapy, in which, the results also showed that the overall survival was similar to ypstage II (16). Although the population was small, our study showed the peculiar long-term outcome of these patients which implied the need to classify this condition into a proper stage. On the other hand, lymph nodes status after preoperative chemotherapy was an important prognostic factor in previous studies (17,18) and our results also showed the robust prognostic value that the survival was significantly different not only in entire model, but also in each adjacent ypN stage. Smyth and colleagues analyzed the data of prospective randomized phase III trial (MAGIC trial) and concluded that the postoperative lymph nodes status but not tumor regression grade (TRG) was the only independent prognostic factor (19). In current study, we described more extremely condition that no residual tumor cells after chemotherapy, which represented the best response to chemotherapy. However, similar results were observed that the overall survival of ypT0N+ was not even better than ypT1-4 with node negative patients. One possible explanation was that the persistent metastatic lymph nodes was related to the residual tumor burden after preoperative chemotherapy, which might affect the outcomes of the disease. Becker, et, al. retrospectively analyzed esophagogastric adenocarcinomas treated by neoadjuvant chemotherapy and the results also demonstrated that ypTNM stage, not TRG, was the independent prognostic factor (17). Hence, positive lymph nodes after neoadjuvant chemotherapy could be an important surrogate to predict the prognosis and its interaction with TRG might be more effective to tailor postoperative therapy.

The limits of this study included: (I) the innate characteristics of retrospective studies. The data of TRG was not included in this study, the relationship between TRG and ypT, ypN stage couldn't be demonstrated. (II) the sample size was relatively small as the low rate of ypT0N+ patients. Large scale study or meta-analysis might be needed to form more solid conclusions.

Conclusions

In conclusion, complete pathological regression of primary lesion (ypT0) was a predictor for long-term outcomes. According to the overall survival, ypT0N0 (pCR) patients might be considered for inclusion in the ypstage I. Meanwhile worse prognosis of ypT0N+ patients was observed in current study and further study was needed to define the best staging category for ypT0N+.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2426). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2020IIT-92). Written informed consent form was obtained from all patients

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