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***Retrospective Study***

**Timing of surgery after neoadjuvant chemotherapy and the impact on outcomes for gastric cancer**

Liu Y *et al*. Timing of surgery after neoadjuvant chemotherapy

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**Abstract**

***AIM***

to evaluate whether the neoadjuvant chemotherapy (NACT)-surgery interval time significantly impacts the pathological complete response (pCR) rate and long-term survival.

***METHEODS***

One hundred and seventy-six patients with gastric cancer undergoing NACT and a planned gastrectomy were selected from the Chinese PLA General Hospital, from January 2011 to January 2017. Univariate and multivariable analyses were used to investigate the impact of NACT-surgery interval time (< 4 wk, 4-6 wk, > 6 wk) on pCR rate and overall survival (OS).

***RESULTS***

The NACT–surgery interval time and clinician T stage were independent predictors of pCR. The interval time of > 6 wk was associated with 74% higher odds of pCR as compared with an interval time of 4-6 wk (*p* = 0.044) and cT3 *vs* cT4 (OR = 2.90, 95%CI: 1.04-8.01, *p* = 0.041). In Cox regression analysis of long-term survival, post-neoadjuvant therapy pathological N (ypN) stage significantly impacted OS, No *vs* N3 (HR = 0.16, 95%CI: 0.37-0.70, *p* = 0.015), and N1 *vs* N3 (HR = 0.14, 95%CI: 0.02-0.81, *p* = 0.029); and on disease-free survival (DFS), N0 *vs* N3 (HR = 0.11, 95% CI 0.24-0.52, *p* = 0.005), and N1 *vs* N3 (HR = 0.17, 95%CI: 0.02-0.71, *p* = 0.020). The surgical procedure also had a positive impact on OS and DFS. The hazard ratio for distal vs. body was 0.12 (95%CI: 0.33-0.42, *p* = 0.001) in OS, and 0.13 (95%CI: 0.36-0.44, *p* = 0.001) in DFS.

***CONCLUSION***

The NACT-surgery interval time was associated with pCR and it had no impact on survival, an interval time of > 6 wk had relatively high odds of pCR.

**Key words:** Gastric cancer; Timing of surgery; Neoadjuvant chemotherapy

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**Core tip:** The impact ofinterval time between completion of neoadjuvant chemotherapy and surgery on pathological complete response (pCR) had been proved in colorectal cancer and esophageal cancer. However, never have a relative research was found in gastric cancer. To evaluate whether the interval time impacts efficiency of neoadjuvant chemotherapy, 176 patients were recruited. The interval time and clinical T stage were proved predictors of pCR. Factors of ypN stage and surgical procedure have a significant impact on the long-terms survival. An interval time of > 6 wk have relatively higher odds of pCR.

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**INTRODUCTION**

Surgery is the only curative treatment for GC. Though we have performed standard surgery in recent years, overall survival (OS) at 5 years for stomach cancer patients remains at ~20%-30%[1]. Since more and more clinical trials have validated the survival benefit of preoperative chemotherapy[2-4], neoadjuvant chemotherapy (NACT) has been gradually accepted by clinicians.

Making patients experience a significant tumor downstaging and even a pathologic complete response (pCR) is the most important goal of NACT. It has been proven that patients who have a pCR may achieve superior OS and fewer local or systemic recurrence than those with a partial or no response[5,6]. Therefore, we have been exploring every potential way to maximize the possibility of attaining a pCR. Since the Lyon R90-01 trials found that patients undergoing an interval of 6-8 wk showed improvement in clinical tumor response and pathologic downstaging compared with a 2-3-wk interval[7], a growing number of studies have proven that a longer interval is significantly related to increased pCR rates, increased tumor downstaging and potential superior OS in rectal cancer[8-11]. However, in esophageal cancer, results are conflicting. Some studies found that a longer interval was associated with higher pCR rates that might improve the prognosis[12,13]; even intervals beyond 12 wk have been thought to be safe[14]. Yet, other studies failed to validate the connection between longer intervals and pCR rates, and found that longer intervals were disadvantageous to long-term OS[15,16]. To our knowledge, the optimal timing of performing surgery after NACT has never been studied in GC. An interval time of 4-6 wk was first practiced in some NACT clinical trials[17,18]. However, an interval of 4-6 wk has never been validated as being optimal. Thus, the aim of this study was to assess the link between NACT–surgery interval time and pCR rates and/or OS.

**MATERIALS AND METHODS**

***Study patients***

This was a retrospective study for which we recruited 216 patients with GC who underwent NACT from the Chinese PLA General Hospital, from January 2011 to January 2017. The criteria for inclusion follow: (1) The gastric cancer was diagnosed using endoscopy and a biopsy. (2) Patients who underwent NACT and a planned gastrectomy. (3) All clinical pathological information was available, including: NACT relevant information, surgical parameters, image information, pathological diagnosis, perioperative therapy, and follow-up data. Exclusion criteria follow: (1) Patients older than 75 years, and (2) patients who ever received chemoradiotherapy. Finally, only 176 patients were included (figure 1). Before NACT, endoscopic ultrasound (EUS) and contrast-enhanced computed tomography (CE-CT) had been performed to assess clinical stage and confirm patients with T2-4N0-3M0 GC, according to the Japanese classification of gastric carcinoma[19].

***NACT and surgery***

Most patients (*n* = 167) received 2-4 cycles of a SOX regimen (S-1 80 mg/m2/d, PO, days 1-14, and oxaliplatin 130 mg/m2/d, IV, infusion on day 1), which is widely used in Asia[20]; the remaining patients (*n* = 9) received a XELOX regimen (capecitabine 1000 mg/m2/d, PO, days 1–14, and oxaliplatin 130 mg/m2/day, IV, infusion on day 1). After two cycles of chemotherapy, the curative effect was evaluated using EUS and CT according to RECIST1.1[21]. A gastrectomy was carried out immediately when imaging showed an observable increase in tumor size or tumor disappearance. If imaging indicated a decrease in tumor size, another one or two cycles of chemotherapy could be performed. The planned operations after NACT were conducted by experienced surgeons. Patients without evidence of metastasis underwent a gastrectomy with a D2 lymphadenectomy. For other patients, the type of operation was decided by a multidisciplinary team. The location of the primary tumor determined whether a proximal, distal, or total gastrectomy was selected.

***Histopathology analysis and follow-up***

The same pathologist microscopically analyzed all resected specimens. Patients with ypT0N0M0 GCs were defined as having a pCR and all others were defined as not having a pCR[11]. Clinical examinations and abdomen CT were performed every 6 mo for 3 years. Digestive endoscopy was performed at least once a year. In March 2017, we confirmed the survival status of patients and the median follow-up time was 42 mo (range, 2-74). Follow-up data were completed for all recruited patients.

***Primary objective and secondary objective***

The primary objective was to evaluate the impact of NACT–surgery interval time to pCR rate and the optimal timing of operation. Our secondary objective was to determine the association between NACT–surgery interval time and 3-year OS or disease-free survival (DFS). For that purpose, of the 171 patients who were admitted from January 2011 to March 2014, 121 were selected.

***Statistical analyses***

We used the chi-squared test or Fisher’s exact test for binary and categorical variables, and ANOVA or t-tests for continuous variables, as appropriate. Patients were compared between the three groups at baseline and postsurgery, and for tumor characteristics. A bivariate analysis between patients, tumors and surgical characteristics, and pCR status was conducted. A tumor and treatment characteristics that achieved a *p* value < 0.2 in univariate analysis were included in the multivariable analysis. Logistic regression was used to model the effects of optimal interval time on the odds of having a pCR, and factors independently associated with pCR were determined using a stepwise procedure. The Kaplan–Meier method was used to estimate survivor functions and the log-rank test was used for the comparison of survival curves. Multivariate analysis using cox proportional hazards regression analysis with a stepwise procedure was performed to investigate independent factors of survival.

All the statistical analysis was performed using IBM® SPSS® Statistics version 22.0 software. The hazard ratio (HR) and 95% confidence interval (95%CI) were reported and used to assess the relationship between pCR rate and survival for each independent factor.

**RESULTS**

Among the 176 patients, 111 (63%) had an NACT–surgery interval time < 4 wk, 48 (27%) had an interval time of 4-6 wk, and 17 (9.7%) had an interval time > 6 wk. The median age was 57 years (range, 21-75 years) and the male to female ratio was 3.5/1. Characteristics of the study cohort are summarized in Table 1. Patient characteristics, tumor characteristics, and surgical procedure were compared among the three groups (< 4 wk, 4-6 wk, and > 6 wk). Age (*p* = 0.014), tumor differentiation (before NACT) (p=0.000), cT stage (*p* = 0.006) and ypT stage (*p* = 0.045) were significantly different among the three groups. Forty (22.7%) patients had achieved a pCR; the proportion of pCRs was 67.5% for those with a NACT–surgery interval time of < 4 wk, 15% for those with a NACT-surgery interval time of 4-6 wk, and 17.5% for those with a NACT–surgery interval time of > 6 wk.

***Primary endpoint: Impact of NACT–surgery interval time on having a pCR***

Table 1 also shows the bivariate association between pCR and patient characteristics, tumor characteristics, and surgical procedure. NACT–surgery interval time (*p* = 0.043), differentiation (before NACT) (*p* = 0.032), cT stage (*p* = 0.027), cN stage (*p* = 0.012), tumor location (*p* = 0.044) and surgical procedure (*p* = 0.002) were significantly different between pCR and no pCR.

Factors that have achieved *p* value < 0.2 in univariate analysis were selected for multivariate analysis, including gender, NACT–surgery interval time, cT stage, cN stage, tumor diameter. Finally, the multivariate analysis (table 2) showed that a NACT–surgery interval time of 4-6 wk was associated with a 74% lower change of having a pCR as compared with an NACT–surgery interval time of > 6 wk (*p* = 0.044) and cT3 *vs* cT4 (OR = 2.90, 95%CI: 1.04-8.01, *p* = 0.041).

***Secondary endpoints: Impact of NACT–surgery interval time on OS and DFS***

Kaplan–Meier analyses for 3-year OS and DFS are presented in figure 2, respectively. There was no significant difference among the three survival curves for both OS and DFS according to the log-rank test. The median OS was 41.5 mo (range, 20.0-61.8 mo) and median DFS was 39.5 mo (range, 0-61.8 mo).

Recurrence was experienced by 29.5% of patients. As show in table 3, NACT–surgery interval time was not found to be independently associated with OS or DFS. Independent factors associated with OS were ypN stage, N0 *vs* N3 (HR = 0.16, 95%CI: 0.37–0.70, *p* = 0.015), N1 *vs* N3 (HR = 0.14, 95%CI: 0.02-0.81, *p* = 0.029), and surgical procedure, distal gastrectomy *vs* total gastrectomy (HR: = 0.12, 95%CI: 0.33-0.42, *p* = 0.001). For DFS, independent factors were also ypN stage and surgical procedure.

**DISCUSSION**

The impact of the NACT–surgery interval on pCR and survival has been proven in rectal cancer and esophageal cancer[8,14]. But, the optimal NACT–surgery interval time and its association with survival, to the best of our knowledge, has never been investigated in GC. Similar to what was found in rectal cancer, the present study’s results suggest that a NACT-surgery interval time of > 6 wk has a positive impact on pCR compared with one of 4-6 wk or < 4 wk. But, the NACT–surgery interval time did not have an impact on either OS or DFS.

To determine the group’s cutoff level, we performed a curve of cumulative proportion of pCR by interval weeks (figure 3). The curve shows that the slope is highest when the interval time is < 4 wk, and 4 and 6 wk are points of inflection. Meanwhile, the interval time for NACT-surgery is commonly 4-6 wk, which is what clinicians in China have adopted. Thus, to prove whether an interval time for NACT–surgery of 4-6 wk is optimal, after taking all factors into consideration, we divided the population into three groups by the cutoff levels of 4 and 6 weeks.

The impact of NACT–surgery interval time on having a pCR is the primary objective that we wanted to address. We defined pCR as T0N0M0, and partial response (PR) was not included in this study. This is because PR, which is confirmed using imaging according to RECIST[21], is more subjective and hence, more difficult to confirm than CR. In table 1, characteristics of age and tumor differentiation (before NACT) are significantly different among the three groups. The average age is highest in the > 6 wk group and lowest in the < 4 wk group. The result suggests that older patients may need a longer recovery period from NACT. In the subsequent univariate and multivariable analysis, age has been shown to have no impact on pCR and long-term outcomes. With respect to tumor differentiation, previous studies showed that the more differentiated a tumor, the higher the pathology response rate when patients were treated with a XELOX regimen[22,23]. However, results from our univariate analysis contradict these previous findings. The factors of NACT–surgery interval time, differentiation (before NACT), cT stage, cN stage, tumor location and surgical procedure are significantly different between the pCR group and none pCR group. We had not included surgical procedure into univariate analysis, for the reason that the pCR status had been determined before surgery. The next multivariable analysis has proved that NACT-surgery interval time and cT stage was independent factors associated with having a pCR. Compared with cT4 stage, patients with lower cT stage of cT2 or cT3 was more likely to achieve pCR, though cT2 stage has no significant difference compared to cT3 stage. It is consistent with a previous study[24], which showed that lower T and N stage were linked with higher likelihood of pCR. Patients with a NACT–surgery interval time of 4–6 wk had lower odds of having a pCR than those with an interval time of > 6 wk (*p* = 0.044). Although a NACT–surgery interval time of <4 weeks was associated with 49% lower chance of patients having a pCR as compared with an interval time of > 6 wk, the result was not statistically significant (*p* = 0.521). From these outcomes and the associations among them, we can conclude that the NACT–surgery interval time of > 6 wk was the optimal interval time and had a positive impact on pCR as compared with the other groups.

This result is consistent with those from previous rectal and esophageal cancer studies[25-28], and it may be a common rule in gastrointestinal malignancies. Though many studies have shown that there is a positive impact from delaying the NACT–surgery interval time on pCR rate and short-term outcomes, the underlying mechanism of this phenomenon has never been discussed. We hypothesize that it may be the result of multiple factors, including the ongoing effect of the radiochemotherapy, changes in the tumor microenvironment, and recovery of immunity from chemotherapy. Additional basic medical studies may be needed to explain it.

The association between NACT–surgery interval time and long-term outcomes was also investigated. The survival curves of the three groups intersected at certain points and the log-rank test did not find any statistical significance among the curves (figure 2). Both for OS and DFS, Cox regression analysis showed that the NACT-surgery interval time and pCR (it is reflected by ypT0 status) had no impact on survival. This result is contrary to our expectation because pCR is deemed to have a positive impact on survival. Meredith *et al*[29] and Abdul-Jalil *et al*[30] both reported that pCR was an independent factor for OS and DFS. We thought that the small sample size may be the limitation. Regarding the NACT-surgery interval time, many previous studies in esophageal cancer proved that the interval time did not have any effect on survival[13,15,31], while some studies in rectal cancer reached an opposite conclusion[26,28]. Our result is consistent with studies in esophageal cancer. What was shown was that ypN stage had a significant impact on OS and DFS. This result aligns with those from previous studies[32,33]. The surgical procedure is also an independent factor that can influence OS and DFS. Patients on whom a distal gastrectomy was performed had a significant difference in survival compared with patients on whom a total gastrectomy was performed. The reason for this result may be that patients who undergo a distal gastrectomy have a greater chance of having a pCR. And also, may be the difference of surgical methods itself.

There were some limitations to our study. Its retrospective nature may induce some bias. Our relatively short follow-up time for survival (3-year estimates) and the absence of information regarding diseases not treated in the PLA General Hospital after the operation may have impacted our results. Also, our single institute research can’t avoid sampling bias and may not be representation. The small sample size was the biggest limitation, the number of patients with interval time > 6 wk was not sufficient to explore more timing groups or the maximum interval time (such as 6-8 wk, 8-12 wk, > 12 wk). A future randomized control trial with a larger sample size from multiple healthcare institutes may be needed to validate our results.

To conclude, the NACT-surgery interval time of > 6 wk can increase the chance of a pCR, but the NACT-surgery interval time does not have an impact on long-term survival.

**Article Highlights**

***Research background***

The impact of the interval time from the completion of neoadjuvant chemotherapy (NACT) to surgery on pathological complete response (pCR) and survival has been proved in rectal cancer and esophageal cancer. But, the optimal NACT-surgery interval time and its association with survival, to the best of our knowledge, has never been investigated in gastric cancer. This study can provide evidence for the timing of surgery and patients with neoadjuvant chemotherapy may benefit from it.

***Research motivation***

To investigate whether the interval time between NACT and surgery have an impact on pCR was our main topic. The investigation lays a foundation for the further RCT researches.

***Research objectives***

There were two objectives in this study. The primary objective was to evaluate the impact of NACT-surgery interval time to pCR rate and the optimal timing of operation. The secondary objective was to determine the association between NACT–surgery interval time and 3-year OS or disease-free survival (DFS). If the impacts are existent, more further researches will focus on the investigation of optimal interval time and these evidences will bring a change in treatment plan of GC patients with neoadjuvant chemotherapy.

***Research methods***

This is a retrospective study, we realized our objectives through data analysis using bivariate analysis, logistic regression analysis and cox proportion hazards regression. These methods are routinely used in studies and have high stability.

***Research results***

The impact of the NACT-Surgery interval time on pCR has been proved and the interval time of > 6 wk can increase the chance of a pCR. Clinical T stage also have an impact on pCR. The independent predictors of long-terms survival are ypN stage and surgical procedure. These findings firstly proved the impact of the NACT-Surgery interval time on pCR in gastric cancer and give a reference for the optimal interval time. The further investigations of accurate optimal interval time are needed.

***Research conclusions***

We firstly investigated and found the impact of the NACT-Surgery interval time on pCR, the optimal interval time may be of > 6 wk. This result is consistent with those from previous rectal and esophageal cancer studies, we hypothesize that it may be the result of multiple factors, including the ongoing effect of the radiochemotherapy, changes in the tumor microenvironment, and recovery of immunity from chemotherapy. Additional basic medical studies may be needed to explain it.

***Research perspectives***

Further researches, either retrospective nature or prospective nature, need to investigate more interval time groups with a large sample size. Also, it is meaningful to investigate the mechanism of this finding through basic medical studies.

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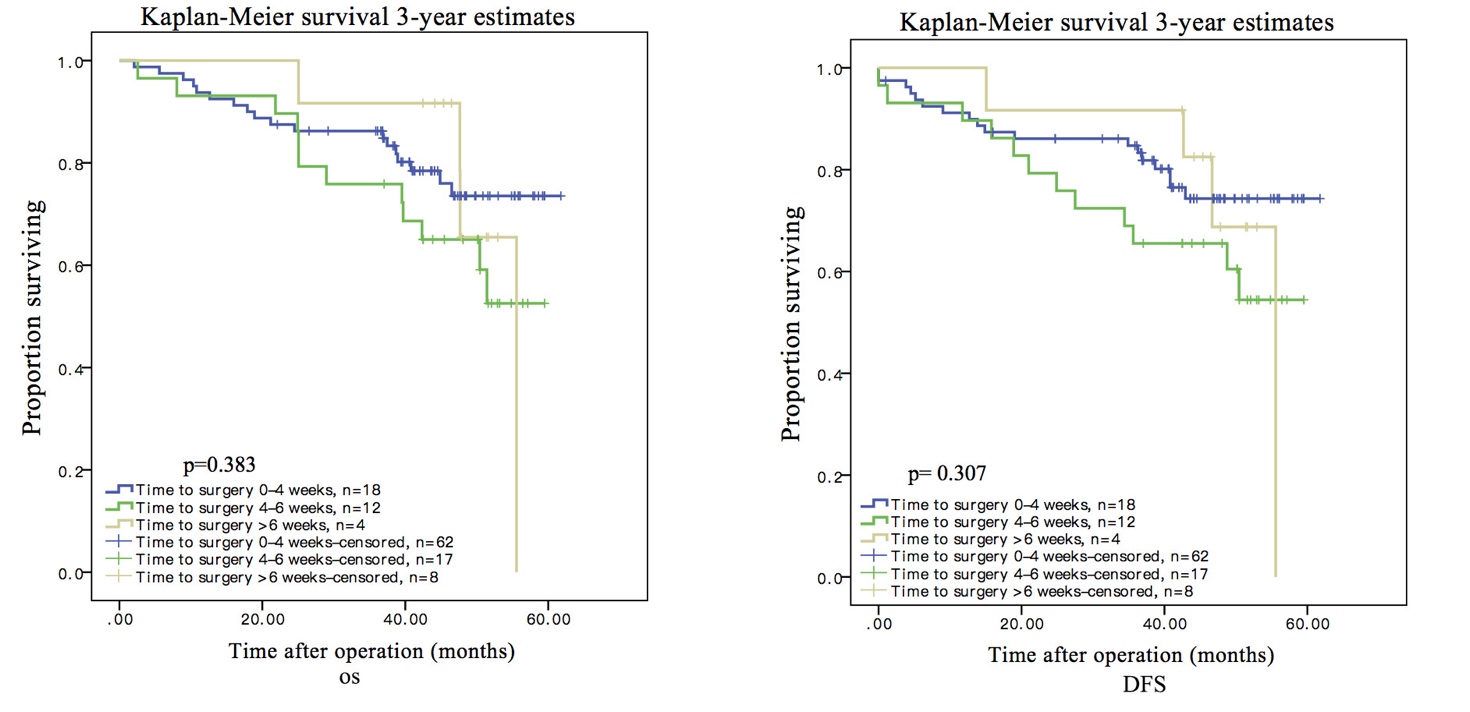
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**Figure l Inclusion diagram.**

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**Figure 2 Overall survival and disease-free survival curves of three groups.** OS: Overall survival; DFS: disease-free survival.

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**Figure 3 Cumulative frequency of pathological complete remission by neoadjuvant chemotherapy to surgery interval time.** NACT: Neoadjuvant chemotherapy.

**Table 1 Demographic and tumor characteristics according to the neoadjuvant chemotherapy-surgery interval time and pathological complete response statues *n* (%)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **< 4 wk (*n* = 111)** | **4-6 wk (*n* = 48)** | **> 6 wk (*n* = 17)** | ***P* value** | **pCR (*n* = 40)** | **No pCR (*n* = 136)** | ***P* value** |
| Age, yr, mean ± SD | 55.5585 ± 10.8079 | 59.7916 ± 9.7891 | 61.5882 ± 9.5985 | 0.014 | 57.375 ± 9.862354 | 57.27206 ± 10.88013 | 0.908 |
| Sex |  |  |  | 0.974 |  |  | 0.174 |
| Male | 87 (78.38) | 37 (77.08) | 13 (76.47) |  | 28 (70.00) | 109 (80.15) |  |
| Female | 24 (21.62) | 11 (22.92) | 4 (23.53) |  | 12 (3.00) | 27 (19.85) |  |
| Chemotherapy cycles |  |  |  | 0.692 |  |  | 1.000 |
| < 4 | 39 (35.14) | 17 (35.42) | 4 (23.53) |  | 14 (35.00) | 46 (33.82) |  |
| ≥ 4 | 72 (64.86) | 31 (64.58) | 13 (76.47) |  | 26 (65.00) | 90 (66.18) |  |
| ASA, yr, mean ± SD |  |  |  | 0.083 |  |  | 0.467 |
| 1 | 8 (7.21) | 1 (2.8) | 2 (11.76) |  | 4 (10.00) | 7 (5.15) |  |
| 2 | 97 (87.39) | 39 (81.25) | 15 (88.24) |  | 32 (80.00) | 119 (87.50) |  |
| 3 | 6 (5.40) | 8 (16.67) | 0 |  | 4 (10.00) | 10 (7.35) |  |
| Histology (before NACT) |  |  |  | 0.398 |  |  | 0.658 |
| Tubular adenocarcinoma | 90 (81.08) | 40 (83.33) | 15 (88.24) |  | 34 (85.00) | 111 (81.62) |  |
| Mucinous | 10 (9.01) | 1 (2.08) | 0 (0.00) |  | 1 (2.50) | 10 (7.35) |  |
| Signet ring cell | 9 (9.11) | 4 (8.33) | 1 (5.88) |  | 3 (7.50) | 11 (8.09) |  |
| mixed type1 | 2 (1.80) | 3 (6.25) | 1 (5.88) |  | 2 (5.00) | 4 (2.94) |  |
| Differentiation (before NACT) |  |  |  | 0.000 |  |  | 0.032 |
| Well | 2 (1.80) | 0 (0.00) | 15 (88.24) |  | 2 (5.00) | 0 (0.00) |  |
| Moderate | 28 (25.23) | 10 (20.83) | 1 (5.88) |  | 10 (25.00) | 35 (25.74) |  |
| Poorly | 81 (72.97) | 38 (79.17) | 1 (5.88) |  | 28 (79.00) | 101 (74.26) |  |
| cT stage |  |  |  | 0.006 |  |  | 0.027 |
| 2 | 31 (27.93) | 17 (35.42) | 6 (35.29) |  | 15 (37.50) | 39 (28.68) |  |
| 3 | 24 (21.62) | 19 (39.58) | 8 (47.06) |  | 16 (40.00) | 35 (19.85) |  |
| 4 | 56 (50.45) | 12 (25.00) | 3 (17.65) |  | 9 (22.50) | 62 (51.47) |  |
| cN stage |  |  |  | 0.170 |  |  | 0.012 |
| Positive | 89 (80.18) | 33 (68.75) | 11 (64.71) |  | 24 (60.00) | 109 (88.97) |  |
| Negative | 22 (19.82) | 15 (31.25) | 6 (35.29) |  | 16 (40.00) | 27 (11.03) |  |
| Tumor location |  |  |  | 0.650 |  |  | 0.044 |
| Upper | 45 (40.54) | 23 (47.92) | 6 (35.29) |  | 10 (25.00) | 64 (47.06) |  |
| Middle | 16 (14.41) | 7 (14.58) | 2 (11.76) |  | 6 (15.00) | 19 (13.97) |  |
| Lower | 45 (40.54) | 14 (29.17) | 7 (41.18) |  | 22 (55.00) | 44 (32.35) |  |
| Diffuse type2 | 5 (4.51) | 4 (8.33) | 2 (11.76) |  | 2 (5.00) | 9 (6.62) |  |
| Tumor diameter (before NACT) |  |  |  | 0.134 |  |  | 0.069 |
| ≤ 2 cm | 15 (13.51) | 8 (16.67) | 2 (11.76) |  | 7 (17.50) | 18 (2.21) |  |
| 2-5 cm | 50 (45.05) | 21 (43.75) | 13 (76.47) |  | 24 (60.00) | 60 (69.85) |  |
| ≥ 5 cm | 46 (41.44) | 19 (39.58) | 2 (11.76) |  | 9 (12.50) | 58 (27.94) |  |
| Surgical procedure |  |  |  | 0.363 |  |  | 0.002 |
| Proximal gastrectomy | 21 (18.92) | 10 (20.83) | 2 (11.76) |  | 9 (22.50) | 24 (17.65) |  |
| Distal gastrectomy | 32 (28.83) | 10 (20.83) | 8 (47.06) |  | 19 (47.50) | 31 (22.79) |  |
| Total gastrectomy | 58 (52.25) | 28 (58.33) | 7 (41.18) |  | 12 (30.00) | 81 (59.56) |  |
| NACT-surgery interval time |  |  |  |  |  |  | 0.043 |
| < 4 wk |  |  |  |  | 27 (67.50) | 84 (61.76) |  |
| 4-6 wk |  |  |  |  | 6 (15.00) | 42 (30.88) |  |
| > 6 wk |  |  |  |  | 7 (17.50) | 10 (7.35) |  |
| ypT stage |  |  |  | 0.045 |  |  |  |
| 0 | 27 (24.32) | 6 (12.50) | 7 (41.18) |  |  |  |  |
| 1 | 7 (6.31) | 9 (18.75) | 3 (17.65) |  |  |  |  |
| 2 | 25 (22.52) | 6 (12.50) | 2 (11.76) |  |  |  |  |
| 3 | 38 (34.23) | 15 (31.25) | 4 (23.53) |  |  |  |  |
| 4 | 14 (12.61) | 12 (25.00) | 1 (5.88) |  |  |  |  |
| ypN stage |  |  |  | 0.187 |  |  |  |
| 0 | 67 (60.30) | 23 (47.92) | 14 (82.35) |  |  |  |  |
| 1 | 7 (6.31) | 7 (14.58) | 2 (11.76) |  |  |  |  |
| 2 | 16 (14.41) | 5 (10.42) | 1 (5.88) |  |  |  |  |
| 3a | 14 (12.61) | 8 (16.67) | 0 |  |  |  |  |
| 3b | 7 (6.31) | 5 (10.42) | 0 |  |  |  |  |

1Mixed type: he tumor contains at least two kinds of cancer cell with difference pathological classification, and the proportion of cancer cells in each type is similar; 2Diffuse type: the region of tumor is beyond one part of stomach (three parts of stomach: cardiac and gastric fundus, gastric body, pylorus and gastric antrum). pCR: pathological complete response; NACT: neoadjuvant chemotherapy.

**Table 2 Multivariate logistic analyses identifying independent predictors of pathological complete response**

|  |  |  |  |
| --- | --- | --- | --- |
| **Factors** | **Odds ratio** | **95%CI** | ***P* value** |
| Sex |  |  |  |
| Male *vs* female | 1.76 | 0.74-4.18 | 0.201 |
| NACT-Surgery interval time |  |  |  |
| < 4 wk *vs* > 6 wk | 0.69 | 0.22-2.13 | 0.521 |
| 4-6 wk *vs* > 6 wk | 0.26 | 0.07-0.96 | 0.044 |
| cT stage |  |  |  |
| T2 *vs* T4 | 1.99 | 0.70-5.68 | 0.200 |
| T3 *vs* T4 | 2.90 | 1.04-8.01 | 0.041 |
| cN stage |  |  |  |
| Positive *vs* negative | 2.12 | 0.90-4.97 | 0.086 |
| Tumor diameter (before NACT) |  |  |  |
| ≤ 2 cm *vs* ≥ 5 cm | 1.60 | 0.44-5.80 | 0.472 |
| 2-5 cm *vs* ≥ 5 cm | 1.58 | 0.60-4.14 | 0.354 |

NACT: neoadjuvant chemotherapy.

**Table 3 Multivariable analyses identifying independent predictors of overall survival and disease-free survival**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Independent predictors** | **3-yr estimate (overall survival)** | | | **3-yr estimate (disease free survival)** | | |
| **HR** | **95%CI** | ***P* value** | **HR** | **95%CI** | ***P* value** |
| NACT-Surgery interval time |  |  |  |  |  |  |
| < 4 wk *vs* > 6 wk | 0.49 | 0.11-2.129 | 0.340 | 0.43 | 0.10-1.85 | 0.258 |
| 4-6 wk *vs* > 6 wk | 0.99 | 0.24-4.06 | 0.985 | 0.93 | 0.23-3.80 | 0.922 |
| Ages |  |  |  |  |  |  |
| ≤ 60 *vs* > 60 | 0.90 | 0.34-2.37 | 0.833 | 0.84 | 0.32-2.19 | 0.720 |
| Sex |  |  |  |  |  |  |
| Female *vs* Male | 1.27 | 0.40-4.04 | 0.688 | 1.24 | 0.39-3.99 | 0.716 |
| Histology (before NACT) |  |  |  |  |  |  |
| Tubular adenocarcinoma *vs* mixed type | 2.56 | 0.24-26.94 | 0.433 | 2.25 | 0.22-22.56 | 0.491 |
| Mucinous *vs* mixed type | 3.79 | 0.21-70.55 | 0.372 | 3.12 | 0.18-53.99 | 0.435 |
| Signet ring cell *vs* mixed type | 5.71 | 0.40-81.22 | 0.199 | 4.99 | 0.37-66.54 | 0.224 |
| Differentiation (before NACT) |  |  |  |  |  |  |
| Well and moderate *vs* poorly | 2.49 | 0.99-6.24 | 0.052 | 2.45 | 0.98-6.11 | 0.054 |
| cT stage |  |  |  |  |  |  |
| T2 *vs* T4 | 1.51 | 0.42-5.39 | 0.524 | 1.67 | 0.48-5.84 | 0.422 |
| T3 *vs* T4 | 0.99 | 0.31-3.16 | 0.980 | 0.98 | 0.31-3.11 | 0.968 |
| cN stage |  |  |  |  |  |  |
| Positive *vs* negative | 0.45 | 0.13-1.62 | 0.221 | 0.49 | 0.14-1.74 | 0.270 |
| Tumor diameter (before NACT) |  |  |  |  |  |  |
| ≤ 2 cm *vs* ≥ 5 cm | 3.16 | 0.61-16.45 | 0.171 | 2.88 | 0.57-14.65 | 0.202 |
| 2-5 cm *vs* ≥ 5 cm | 1.91 | 0.72-5.10 | 0.196 | 1.74 | 0.65-4.65 | 0.267 |
| Tumor location |  |  |  |  |  |  |
| Upper *vs* diffuse type | 1.04 | 0.15-7.33 | 0.973 | 0.99 | 0.14-6.98 | 0.989 |
| Middle *vs* diffuse type | 1.11 | 0.16-7.78 | 0.915 | 1.16 | 0.17-8.05 | 0.879 |
| Lower *vs* diffuse type | 4.41 | 0.78-25.18 | 0.095 | 3.94 | 0.69-22.50 | 0.123 |
| Surgical procedure |  |  |  |  |  |  |
| Proximal gastrectomy *vs* total gastrectomy | 0.69 | 0.17-2.73 | 0.593 | 0.79 | 0.20-3.07 | 0.729 |
| Distal gastrectomy *vs* total gastrectomy | 0.12 | 0.33-0.42 | 0.001 | 0.13 | 0.36-0.44 | 0.001 |
| ypT stage |  |  |  |  |  |  |
| T0 *vs* T4 | 1.04 | 0.15-7.20 | 0.968 | 1.27 | 0.18-9.08 | 0.811 |
| T1 *vs* T4 | 0.57 | 0.09-4.14 | 0.601 | 0.588 | 0.86-4.04 | 0.589 |
| T2 *vs* T4 | 1.15 | 0.24-5.53 | 0.858 | 1.29 | 0.26-6.46 | 0.756 |
| T3 *vs* T4 | 0.60 | 0.15-2.09 | 0.387 | 0.59 | 0.16-2.18 | 0.425 |
| ypN stage |  |  |  |  |  |  |
| N0 *vs* N3 | 0.16 | 0.37-0.70 | 0.015 | 0.11 | 024-0.52 | 0.005 |
| N1 *vs* N3 | 0.14 | 0.02-0.81 | 0.029 | 0.17 | 0.02-0.71 | 0.020 |
| N2 *vs* N3 | 0.47 | 0.11-1.98 | 0.302 | 0.40 | 0.09-1.67 | 0.208 |

NACT: neoadjuvant chemotherapy.