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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Longer Time Interval from Neoadjuvant Chemoradiation to Surgery is Associated with Poor Survival for Patients Without Clinical Complete Response in Oesophageal Cancer

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ABSTRACT

Background. The optimal interval between neoadjuvant therapy and oesophagectomy for oesophageal cancer remains controversial.

Methods. Patients with locally advanced oesophageal squamous cell carcinoma (ESCC) who received neoadjuvant chemoradiotherapy followed by oesophagectomy between June 2017 and December 2020 were prospectively enrolled and retrospectively analysed. Patients were divided into two groups: timely (group A; < 10 weeks) and delayed (group B; ≥ 10 weeks) surgery groups. Survival was the primary outcome, and tumour response and post-operative complications were the secondary outcomes.

Results. Overall, 224 patients were recruited; 116 patients (51.8%) underwent timely surgery within 10 weeks (group A), and 108 patients (49.2%) underwent delayed surgery over 10 weeks (group B) after chemoradiotherapy. In patients with clinical complete response (cCR), two groups had no significant difference of survival benefit (P = 0.618). However, in patients without cCR, delayed surgery was associated with poor survival (P = 0.035) and cancer progression (P = 0.036). A total of 40 patients (34.5%) in group A and 54 patients (50.0%) in group B achieved pCR (P = 0.019). pCR rates were significantly different across the four groups and increased over time (P = 0.006).

Conclusions. Patients with a prolonged time interval from neoadjuvant chemoradiation to surgery had higher pCR rates. For patients with cCR to neoadjuvant chemoradiation, the time interval to surgery can be safely prolonged for at least 10 weeks. However, for patients with non-cCR to neoadjuvant chemoradiation, delayed surgery is associated with poor survival, and surgery should be performed within 10 weeks of neoadjuvant chemoradiation.

For locally advanced oesophageal squamous cell carcinoma (ESCC), addition of neoadjuvant chemoradiotherapy (NACR) to oesophagectomy improves long-term survival and locoregional control and is strongly recommended according to National Comprehensive Cancer Network guidelines.[1–4] The time interval from NACR to oesophagectomy has been set at 4–6 or 6–8 weeks in clinical practice.[3–6] However, Shapiro et al. observed the CROSS trial cohort and concluded that time to surgery (TTS) could be safely prolonged to at least 12 weeks and that the prolonged TTS increased the rate of pathological complete response (pCR).[7] There are unavoidable reasons for delaying TTS after NACR, including patients' poor physical condition, poor nutritional status, uncontrolled comorbidities, severe treatment-related adverse events such as radiation-related pneumonia and cardiotoxicity, and barriers to care during the COVID-19 pandemic.

Currently, evidence on the optimal TTS after neoadjuvant therapy for oesophageal cancer remains unclear and controversial. Some published studies concluded that prolonged TTS after neoadjuvant therapy led to a higher rate of pCR without increasing the post-operative morbidity

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and had no impact on long-term survival.[7,8] On the contrary, some researchers reported that prolonged TTS after neoadjuvant therapy could reduce tumour recurrence.[9] Recently, a randomised controlled trial (RCT) demonstrated that there was no association between the neoadjuvant therapy–surgery time interval and short-term post-operative outcomes.[10] In theory, patients with prolonged TTS might have relief from neoadjuvant therapy and achieve a higher pCR rate because of the prolonged effect of neoadjuvant therapy. However, it might be advantageous for local tumour growth and higher rate of morbidity.

In this study, our primary aim was to investigate whether prolonged TTS affected survival outcomes, and the secondary aim was to evaluate whether there were differences in pCR, tumour response and post-operative complications in patients with locally advanced ESCC who were treated with NACR followed by oesophagectomy.

PATIENTS AND METHODS

Patients and Study Design

This was a single-centre retrospective control study. The data were retrieved from the electronic medical record system. It was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[11] This study was approved by the Institutional Review Board of our hospital (2021-909), and the need for informed consent was waived for all patients. This study was retrospectively registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=169557), where the protocol can be found. The registration ID is ChiCTR2200059906.

Inclusion and Exclusion Criteria

We retrospectively searched our prospective cohort database for all patients who underwent NACR followed by oesophagectomy between June 2017 and December 2020. The inclusion criteria were as follows: resectable squamous cancer, clinical stages T1N1–2M0 or T2–T4aN0–2M0, patient age of 18–75 years old with Eastern Cooperative Oncology Group performance status score of ≤ 2, completed 2 cycles of cisplatin and paclitaxel or cisplatin and carboplatin, completed a total radiation dose of 40–50.4 Gy (1.8–2.0 Gy per fraction), and receiving minimally invasive three-incision McKeown surgery. To minimise potential heterogeneity caused by employing different surgeons, we included only three experienced surgeons (Dr. Chen LQ, Dr. Yuan Y and Dr. Hu Y) who perform more than 100 oesophagectomies annually.

The exclusion criteria were presence of gastric and gastro-oesophageal cancer, upper tumour border above 20 cm from the incisors, local or distant progression after the end of chemoradiotherapy, salvage oesophagectomy and missing data on baseline characteristics, outcomes, or post-operative follow-up. Patients who received planned definitive chemoradiotherapy followed by surgery were considered as salvage oesophagectomy cases. Patients receiving planned NACR, with clinical complete response (cCR) to chemoradiation, initially chose to receive surveillance rather than surgery and then underwent surgery after evidence of recurrence. These cases were also considered as salvage cases. However, patients receiving planned NACR, with stable disease on restaging, were not considered as salvage cases regardless of the time interval between NACR and surgery.

Staging Before NACR

Patients' staging was routinely examined by neck, chest and abdominal contrast-enhanced computed tomography (CT), and oesophagoscopy. Cardiopulmonary function was evaluated before neoadjuvant treatment initiation.

Clinical Evaluation of the Effect of NACR

At 4–6 weeks after the end of neoadjuvant therapies, clinical restaging and tumour response to NACR were evaluated by endoscopic and radiological findings. According to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1), clinical complete response (cCR) was defined as: (1) complete disappearance of the primary tumour lesion and no new lesion, (2) no ulceration (slough) and (3) disappearance of cancer cells in biopsy specimens plus no local progression and distant metastasis on CT scan.[12,13] If there was a sign of local progression and the tumour was resectable, then patients would continue to receive prompt oesophagectomy. Patients with distant metastasis would continue to receive definitive chemoradiotherapy. Therefore, these patients were excluded from the analysis.

Chemoradiotherapy

Generally, NACR includes two cycles of chemotherapy with concurrent radiation. The NACR treatment cycle lasted for 21–28 days (treatment during weeks 1 and 4). Paclitaxel at a dose of 175 mg/m^2 (day 1) was administered intravenously with a combination of cisplatin at a dose of 25 mg/m^2/24 h (days 1–3) or with a combination of carboplatin at a dose of area under the curve 5 (day 1).

Patients received concurrent radiation up to a total dose of 40–50.4 Gy, delivered at a dose of 1.8–2.0 Gy per fraction, starting from day 1 of the first chemotherapy cycle (week 1) and ending at the completion of the second chemotherapy cycle (week 4). All patients received radiotherapy using intensity-modulated radiotherapy. During NACR, patients were assessed for the occurrence of adverse events once a week.

Surgery and Post-operative Management

Patients were scheduled to undergo surgical resection 6–8 weeks after completion of neoadjuvant therapy. Surgical resection was performed using standard minimally invasive three-incision McKeown[14] surgery and two-field lymphadenectomy. For distal oesophageal and junctional cancers and thoracic oesophageal cancers, the standard minimally invasive three-incision McKeown procedure was routinely performed. For gastro-oesophageal anastomosis in the left side of the neck, the hand-sewn double-layer or single-layer technique was performed with an end-to-end or end-to-side configuration.

During the first 5 days of post-operative care, total parenteral nutrition was provided. Oral feeding was continued with a semi-liquid diet until a chest radiograph revealed no signs of anastomotic leakage, and a soft diet was started on post-operative day (POD 9). The patient was discharged from the hospital without tubes on POD 10. After discharge, the patient received complete oral feeding and began a regular diet on POD 21.

Follow-Up

One month after surgery, the patients were examined by chest radiography and underwent adjuvant therapy according to post-operative pathology. Follow-up visits were scheduled 4 months after the operation and every 6 months thereafter, and contrast-enhanced CT scans of the neck, chest and abdomen were performed at each visit.

OUTCOMES

Primary Outcomes

The primary endpoints of this trial were overall survival (OS) and progression-free survival (PFS). Disease recurrence was defined as local (oesophageal bed or anastomotic), locoregional (regional lymph nodes) or distant (distant lymph nodes or distant organs, including the lung, liver and bone). The clinical and pathological stages were referenced from the AJCC/UICC staging system (8th edition).

Secondary Outcomes

The secondary endpoints were histological tumour response measured by the tumour regression score (TRS),[15] pathological complete regression (pCR) rate and post-operative complications, in accordance with the Clavien–Dindo (CD) classification system[16] and oesophagectomy complications consensus group classifications.[17] pCR was defined as absence of tumour cells in the specimen, including lymph nodes (ypT0N0). TRS was graded as follows: grade 0 (complete response), grade 1 (near-complete response), grade 2 (partial response) and grade 3 (poor or no response) (https://cap.org/). Downstaging was defined as a reduction in the tumour, node, metastasis (TNM) stage of pathological staging (pTNM) compared with clinical staging (cTNM).

Statistical Analysis

Data and outcomes were analysed using STATA software (version 16.0; STATA Corporation, College Station, TX, USA), MedCalc (version 20.1; MedCalc software, Ostend, Belgium) and GraphPad Prism 8.0 (San Diego, CA, USA). Continuous variables are expressed as mean ± standard deviation or median [interquartile range (IQR)], and count data are expressed as absolute numbers and percentages. Categorical variables were analysed using the chi-squared test or Fisher's exact test. Continuous variables were analysed using Student's *t*-test or the Mann–Whitney *U* test. Differences were considered statistically significant when the two-sided *P*-value was less than 0.05. Factors independently associated with pCR were determined using logistic regression analysis. The multivariable-adjusted model was used for the analysis of pCR and included pre-specified potential confounders: sex, age, body mass index (BMI), cT stage and cN stage. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards regression model was used for the univariate and multivariable survival analyses. The multivariable survival model was adjusted for pTNM stage, pN stage, pCR and TRS.

Restricted cubic splines (three knots) were used to assess the nonlinearity of the effect of time interval to surgery. Receiver operating characteristic (ROC) curve was constructed to calculate the optimal cut-off and the area under the curve (AUC). The patients were first divided into two groups based on the cut-off point. For the second step of the analysis, we further classified patients according to interval quartiles ($\leq$ 56 days, 57–68 days, 69–91 days and $\geq$ 92 days) and 3-week groups (3 to $\leq$ 6 weeks, 6 to $\leq$ 9 weeks, 9 to $\leq$ 12 weeks and $>$ 12 weeks). The association of interval quartiles and 3-week groups with pCR rates was analysed using the Cochran–Armitage trend test.

RESULTS

Patients' Characteristics

Between June 2017 and December 2020, 447 oesophagectomies were performed after NACR for locally advanced ESCC. A total of 224 patients who met the inclusion criteria were included in this analysis (Supplementary Fig. 1). The median TTS was 69 days (IQR, 56–91 days) (Supplementary Fig. 2). The association of TTS with pCR was not non-linear (P = 0.738) (Supplementary Fig. 3), and ROC curve indicated TTS cut-off point of 10 weeks for pCR (AUC, 0.622, P = 0.001) (Supplementary Fig. 4). Then we divided the patients into two groups according to the optimal cut-off point (10 weeks). A total of 116 patients (51.8%) underwent oesophagectomies within 10 weeks (range, 24–69) (group A), and 108 patients (49.2%) underwent oesophagectomies over 10 weeks (range, 70–145) (group B) after completing chemoradiotherapy. Among patients in the timely surgery group, the median time interval from the end of chemoradiotherapy to surgery was 56 days (IQR, 49–63 days), while the median interval in the delayed surgery group was 92 days (IQR, 77–100 days) ($P < 0.001$).

Most of the patients in the two groups were aged between 62 and 63 years, were predominantly male, and had clinical T3N1 and stage III ESCC with normal BMI (Table 1). In terms of the treatment protocol, the majority of patients (91.4% in group A and 90.7% in group B) completed two cycles of cisplatin and paclitaxel (TP) (P = 0.819). Patients in groups A and B completed radiation with the same median dose of 41.4 Gy (range, 40–50.4; P = 0.183). Moreover, 78 patients (67.2%) in group A and 60 patients (55.6%) in group B completed radiation with a total dose of 40–45 Gy (P = 0.072). Notably, 20 of 116 (17.2%) patients in group A and 15 of 108 (13.9%) patients in group B received adjuvant therapy, with no significant difference (P = 0.489). There were no statistically significant differences in the baseline characteristics of the patients between the two groups.

Primary Outcomes

After a median follow-up time of 28 months [95% confidence interval (CI), 26–31 months] in group A and 25 months (95% CI, 23–28 months) in group B, the OS was similar between the two groups (P = 0.119), as shown in Fig. 1A. The 1-year and 3-year cumulative OS rates were, respectively, 89.3% and 72.0% in group A versus 86.7% and 72.5% in group B (P = 0.687, P = 0.260). In the multivariable analysis, pIII/II and pN+ were significantly associated with survival ($P \leq 0.001$), as shown in Supplementary Table 1. The Kaplan–Meier curve of PFS showed no significant difference in survival benefits between the two groups (P = 0.423) (Fig. 1B). The 1-year and 3-year PFS rates were, respectively, 79.0% and 52.7% in group A versus 77.2% and 56.8% in group B (P = 0.780, P = 0.839).

In our analysis, 83 patients (71.6%) in the timely surgery group and 83 patients (76.9%) in the delayed surgery group achieved a cCR to NACR, along with a similar distribution of TRS (Supplementary Fig. 5). A subgroup survival analysis was conducted after stratification by clinical response to NACR (cCR and non-cCR) to evaluate whether the delayed surgery was rational for patients with cCR. In the subgroup analysis, there were no statistically significant differences in the baseline characteristics of patients between the two time interval groups. As shown in Fig. 2, the Kaplan–Meier curves of OS and PFS suggested no significant difference in survival benefit for patients with a cCR after two different time intervals to surgery (P = 0.618, P = 0.836). However, for patients with non-cCR, delayed surgery was associated with poor survival (P = 0.035) and cancer progression (P = 0.036) (Fig. 3). The 3-year cumulative OS rate for the group that showed non-cCR after NACR was 77.7% in the timely surgery group (median 32 months) versus 47.9% in the delayed surgery group (median 17 months), with a significant difference (P = 0.031).

Secondary Outcomes

Operation and Pathology All patients underwent minimally invasive three-incision oesophagectomy. Of note, 3 of 116 patients in group A and 2 of 108 patients in group B were unexpectedly converted to open surgery owing to severe pleural adhesion. The operation time, blood loss and lymph nodes did not show significant differences between the two groups ($P > 0.05$) (Table 2). In terms of R0 resection, three patients in each group had positive margins of the oesophageal stump microscopically (R1), with no significant difference.

A total of 40 patients (34.5%) in the timely surgery group and 54 patients (50.0%) in the delayed surgery group achieved pCR with a statistically significant difference (P = 0.019), along with a similar distribution of pathological stage. In the analysis of univariable and multivariable logistic models, a $\geq$ 10-week interval [odds ratio (OR) 1.80; 95% CI 1.03–3.15], female sex (OR 2.88; 95% CI 1.30–6.01) and BMI $\geq$ 25 kg/m^2 (OR 2.52; 95% CI 1.27–4.98) were independent predictors of pCR (Supplementary Table 1). However, the TRSs between the two groups showed no significant difference ($P > 0.05$). In the subgroup analysis of patients with a cCR to NACR after two different intervals, the pCR rate for the group that showed after NACR was 65.1% in the delayed surgery

TABLE 1 Characteristics of study patients in both groups

Characteristic	Timely surgery (n = 116)		Delayed surgery (n = 108)		P
	No.	%	No.	%	
Age, years					0.190
Median	62	NA	63	NA	
IQR	56–66	NA	56–67	NA	
Sex					0.434
Male	100	86.2	89	82.4	
Female	16	13.8	19	17.6	
Tumour type					NA
SCC	116	100	108	100	
Tumour location					0.132
Upper	14	12.1	6	5.6	
Middle	67	57.8	74	68.5	
Lower	35	30.2	28	25.9	
BMI, kg/m^2					0.201
$\geq$ 25	19	16.4	27	25.0	
18–24.9	86	74.1	75	69.4	
< 18	11	9.5	6	5.6	
Radiation doses					0.186
40–45 Gy	78	67.2	60	55.6	
45–50 Gy	35	30.2	43	39.8	
50–50.4 Gy	3	2.6	5	4.6	
Chemotherapy					0.819
TP	106	91.4	97	89.8	
TC	10	8.6	11	10.2	
cTNM stage					0.597
II	13	11.2	16	14.8	
III	79	68.1	67	62.0	
IV	24	20.7	25	23.1	
Response to NACR					0.366
cCR	83	71.6	83	76.9	
Non-cCR	33	28.4	25	23.1	
Adjuvant therapy	20	17.2	15	13.9	0.489

BMI body mass index, *NACR* neoadjuvant chemoradiotherapy, *cCR* clinical complete response, *TNM* tumour, node, metastasis, *IQR* interquartile range, *SCC* squamous cell cancer, *TP* cisplatin and paclitaxel, *TC* carboplatin and paclitaxel, *NA* not available

group versus 48.2% in the timely surgery group (P = 0.028).

Post-operative Complications

The post-operative complications in the two groups were similar in terms of anastomotic leakage, anastomotic structure, vocal cord injury, pneumonia, respiratory failure and 30-day mortality, with no significant differences (Table 3). The overall complication rates in accordance with the CD grades were 44.8% in group A and 41.8% in group B. The anastomotic leakage rate was 6.0% in group A and 9.3% in group B (P = 0.362). Respiratory failure occurred in three patients in group A versus four patients in group B, and needed ventilator support (P = 0.714). In total, only one patient in each group had an unexpected reoperation due to post-operative bleeding. One patient in group A and four patients in group B died of anastomotic leakage, while one patient in group B died owing to pneumonia.

Further Analysis

Furthermore, we divided the patients into four groups according to the regular period (3-week group): 3–6 weeks (n = 14), 6–9 weeks (n = 76), 9–12 weeks (n = 72) and > 12

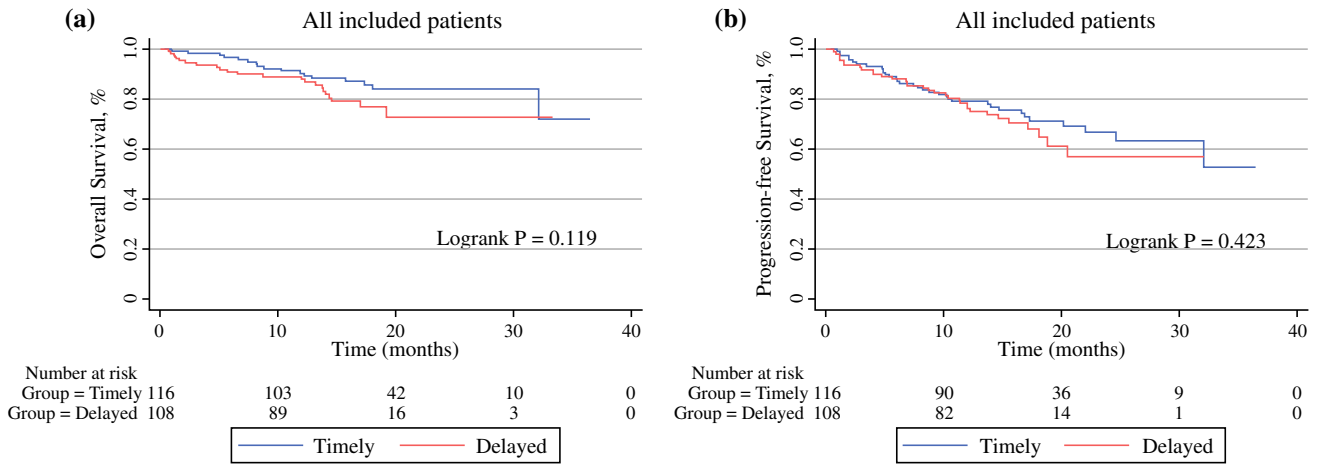

FIG. 1 Kaplan–Meier curves for overall survival in all included patients

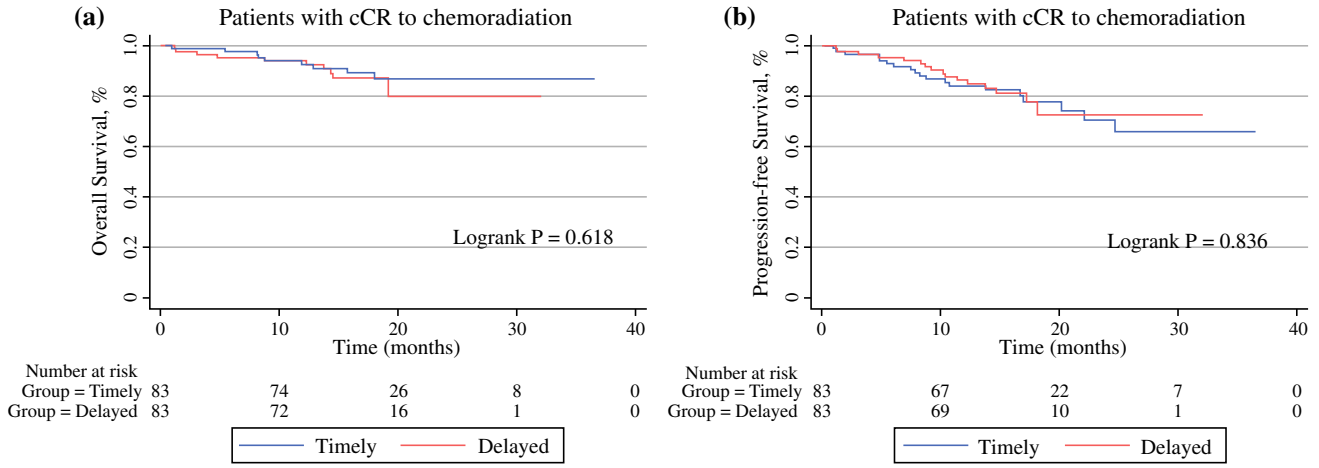

FIG. 2 Kaplan–Meier curves for overall and progression-free survival in patients with clinical complete response (cCR) to neoadjuvant chemoradiotherapy (NACR)

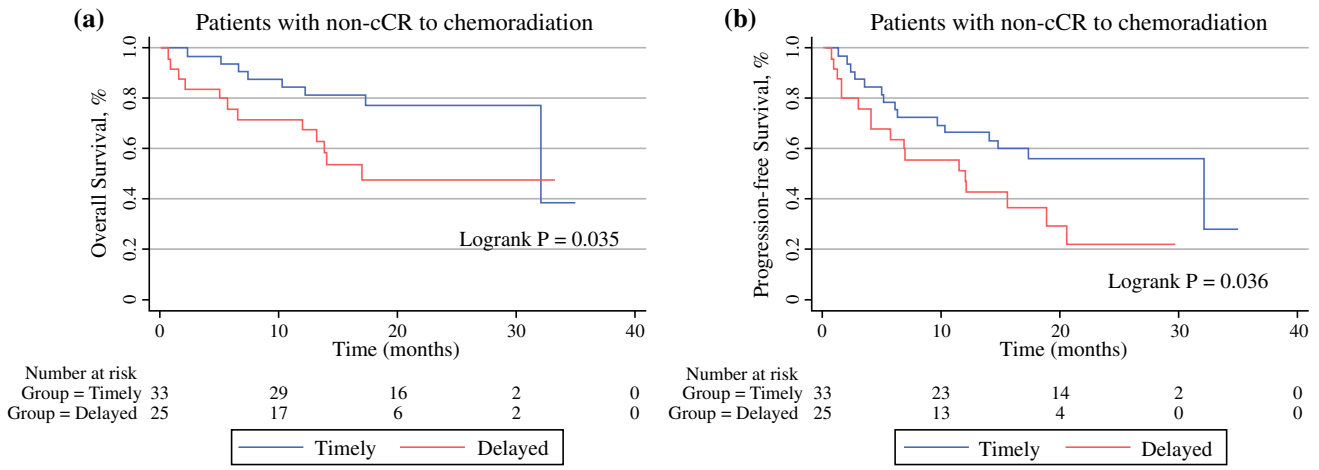

FIG. 3 Kaplan–Meier curves for survival in patients without clinical complete response (non-cCR) to neoadjuvant chemoradiotherapy (NACR)

weeks (n = 62). Among patients who accepted delayed surgery over 9 weeks after completing chemoradiotherapy, 98 (73.1%) patients had a longer interval due to the COVID-19 pandemic and another 16 (11.9%) had a poor

TABLE 2 Operation and pathology data

Characteristics	Timely surgery (n = 116)		Delayed surgery (n = 108)		P
	No.	%	No.	%	
Interval to surgery (days)					0.000*
Median	56	NA	92	NA	
IQR	49–63	NA	77–100	NA	
Operation time (min)	268 ± 43	NA	276 ± 48	NA	0.169
Blood loss volume (ml)					0.186
Median	40	NA	40	NA	
IQR	30–60	NA	30–60	NA	
pCR	40	34.5	54	50.0	0.019*
Downstaging (TNM)	82	70.7	82	75.9	0.377
pTNM stage					0.120
I	58	50.0	70	64.8	
II	16	13.8	8	7.4	
III	37	31.9	25	23.1	
IV	5	4.3	5	4.6	
TRS					0.442
0	46	39.7	54	50.0	
1	18	15.5	15	13.9	
2	44	37.9	35	32.4	
3	8	6.9	4	3.7	
R0 resection					1.000
Yes	113	97.4	105	97.2	
No	3	2.6	3	2.8	
Lymph nodes					0.732
Median	22	NA	21	NA	
IQR	15-25	NA	15–26	NA	
Lymph stations					0.855
Median	11	NA	11	NA	
IQR	9–13	NA	9–13	NA	

IQR interquartile range, *TRS* tumour regression score, *pCR* pathological complete response, *TNM* tumour, node, metastasis, *NA* not available

physical condition after chemoradiotherapy. Other reasons for a delayed time interval to surgery included admitting hospital difficulties (12 patients), perioperative preparation (4 patients), post-NACR hospitalization (2 patients) and patient choice (2 patients). The four groups did not differ significantly in age, sex, tumour location, BMI, radiation doses, planning of chemotherapy, clinical TNM stage, pathological TNM stage or harvested lymph stations aside from harvested lymph nodes (P = 0.023; Supplementary Tables 2 and 3). The pCR rates were 21.5%, 32.9%, 43.1%, and 54.8%, respectively. However, the P-values showed no significant differences across the four groups using the logistic regression model (Supplementary Table 4). Notably, the OR of the pCR rate increased with the time interval. In the Cochran–Armitage trend test, the pCR rates were significantly different among the four groups (P = 0.006; Fig. 4A). There was no difference in OS (P = 0.866) or PFS (P = 0.859) by 3-week intervals (Supplementary Fig. 6).

Additionally, the patients were divided into four groups based on time quartiles: quartile 1 (n = 59), quartile 2 (n = 53), quartile 3 (n = 57) and quartile 4 (n = 55). There were no significant differences in the clinical, surgical and pathological characteristics (Supplementary Tables 5, 6). The pCR rates were 30.5% in the shortest interval quartile (quartile 1) and 54.5% in the longest interval quartile (quartile 4), with a significant difference (OR 2.73; 95% CI 1.27–5.89; P = 0.010; Supplementary Table 4). Similarly, pCR rates were significantly different across the four groups and increased over time (P = 0.009; Fig. 4B). In the analysis of OS and PFS, the interval quartile did not reach a significantly different level (Supplementary Fig. 7).

TABLE 3 Morbidity and mortality rates

Characteristics	Timely surgery (n = 116)		Delayed surgery (n = 108)		P
	No.	%	No.	%	
Anastomotic leakage	7	6.0	10	9.3	0.362
CD grades 1–2	3	2.6	3	2.8	1.000
CD grades 3–4	3	2.6	3	2.8	1.000
CD grade 5	1	0.9	4	3.7	0.199
Anastomotic structure (CD grade 2)	3	2.6	4	3.7	0.714
Vocal cord injury (ECCG type 1)	3	2.6	2	1.9	1.000
Pneumonia	33	28.4	23	21.3	0.217
CD grades 1–2	20	17.2	11	10.2	0.175
CD grades 3–5	13	11.2	11	11.1	1.000
Respiratory failure	3	2.6	4	3.7	0.714
Cardiac complications (CD grades 1–2)	2	1.7	2	1.9	1.000
ICU stay	4	3.4	7	6.5	0.294
Reoperation	1	0.9	1	0.9	1.000
Clavien–Dindo grades					0.313
CD 1–2	28	24.1	22	20.4	
CD 3–4	23	19.8	18	16.7	
CD 5	1	0.9	5	4.8	
Post-operative LOS, d					0.777
Median	11	NA	10	NA	
IQR	8–12	NA	10–13	NA	
30-day mortality	1	0.9	5	4.8	0.107
30-day readmissions	0	0	3	2.8	0.110

LOS length of hospital stay, *IQR* interquartile range, *NA* not available, *CD* Clavien–Dindo, *ICU* intensive care unit, *ECCG* oesophagectomy complications consensus group classifications

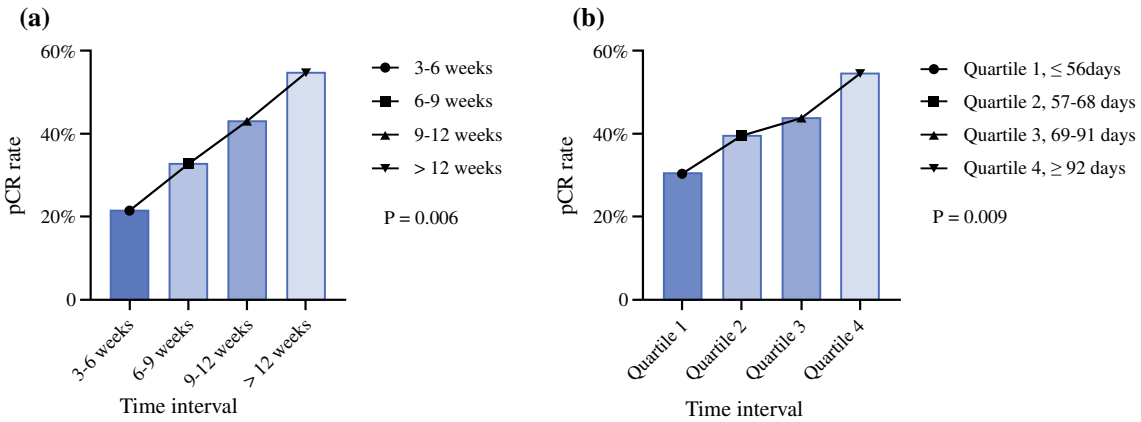

FIG. 4 Association of interval quartiles and 3-week groups with pathological complete response (pCR) rates

DISCUSSION

The present study showed that delayed surgery was associated with poor survival and cancer progression for patients with a non-cCR to NACR. Additionally, an interval of ≥ 10 week independently predicted pathological complete response. The time interval to surgery can be safely prolonged for at least 10 weeks in patients who achieved cCR to neoadjuvant chemoradiation.

The treatment of locally advanced oesophageal cancer is based on multimodal management (neoadjuvant chemo/radiotherapy, adjuvant chemo/radiotherapy, perioperative

chemo/radiotherapy or nanomedicine).[18] Currently, NACR has become the standard treatment for patients with locally advanced oesophageal cancer in many institutions.

In many phase III RCTs of NACR for resectable locally advanced ESCC, patients were scheduled for surgery 4–6 weeks after completion of chemoradiotherapy.[3,4,19] An appropriate time interval may be associated with better tumour regression through apoptosis and necrosis and enable therapy-induced acute inflammation to subside as much as possible, which may enhance tumour resectability and histological tumour response. Conversely, prolonged TTS might lead to residual tumour outgrowth, increased difficulty of surgical resection with a higher post-operative complication rate, and possible worse OS.

Many studies have compared the short-term and long-term outcomes of different time intervals from neoadjuvant therapy to oesophagectomy for locally advanced oesophageal cancer.[7–10,20–22] However, the optimal timing of surgery after chemoradiotherapy is controversial. Despite the confounders of different treatment protocols, several retrospective studies demonstrated that pCR rates, post-operative complications and survival did not differ between the longer and shorter time intervals to surgery,[9,10,22] while two studies[7,8] concluded that the increased time interval to surgery was associated with higher pCR rates, and two studies[20,21] found that patients receiving surgery with longer time intervals had poor survival, with a significant difference. Undoubtedly, patients with higher pCR rates after neoadjuvant therapy have improved survival. Consistent with the findings of previous studies, our results demonstrated that patients achieving pCR had better OS than patients who had residual or microscopic tumours. Although patients with a longer time interval to surgery had a higher pCR rate, it did not translate into better OS in our analysis. The small sample size in each group may be the reason for this conclusion.

However, other studies have suggested that the pCR rate did not differ between longer time intervals and shorter time intervals to surgery.[9,10,22] Our study analysed pCR rates by stratifying patients according to the time elapsed between the end of NACR and surgery. The results demonstrated that patients with more time elapsed from the end of neoadjuvant therapy to surgery had higher pCR rates. This disparity may be attributed to various reasons. A previous study classified the patients into two groups and had a much shorter time interval to surgery, consequently failing to identify any potential significant differences.[9] Different results in these studies may also be affected by inherent biases, such as neoadjuvant therapy regimens, type of operation, and histology. We included only patients with squamous cell carcinoma who completed two cycles of TP (cisplatin and paclitaxel) or TC (carboplatin and paclitaxel), and a total radiation dose of 40–50.4 Gy, and all received minimally invasive McKeown surgery. Thus, our study groups did not differ in treatment-related factors. Shaikh et al. reviewed 88 patients who underwent surgery within 45 days, 46–50 days, 51–63 days, or more than 64 days and 3–6 weeks, 6–9 weeks, 9–12 weeks, or more than 12 weeks following NACR.[8] Similar to our study findings, increased time interval to surgery was associated with higher pCR rates. Chiu et al. included 276 patients with ESCC and divided them into two groups: group A ($\leq$ 8 weeks) and group B ($>$ 8 weeks).[20] pCR rates were similar in each group, with no significant difference. Histological tumour response was measured using the tumour regression grade (TRG) score. However, they found that a longer time interval was associated with a significantly higher residual cancer rate (TRG 3 and TRG 4). In contrast, we also assessed the tumour response using the TRS and found that there was no difference between the two groups. In our analysis, six patients in the timely surgery group scored TRS 0 with pN+; however, no patients in the delayed surgery group scored TRS 0 with pN+. This difference might have caused the disconnection between the pCR rate and TRS.

In terms of survival, Tsang et al. analysed 107 patients with ESCC by dividing them into interval groups, namely, surgery after chemoradiotherapy $\leq$ 64 days and $>$ 64 days, and patients with shorter time interval to surgery had significant survival benefit (5-year OS, 71.7% versus 51%, $P = 0.032$).[21] Kim et al. divided the patient population into two groups by using 8 weeks as a cut-off level and found that OS was similar for the two groups.[22] Chiu et al. reported that delayed surgery was associated with poor survival and surgery should be performed within 8 weeks for patients with a cCR to neoadjuvant chemoradiation.[20] In our analysis, we also initiated a subgroup analysis after stratification by the clinical response to chemoradiation (cCR and non-cCR). We found that OS and PFS rates were similar between the delayed surgery group and the timely surgery group for patients with a good response. However, timely surgery, compared with delayed surgery, was associated with better survival in patients with non-cCR to chemoradiation (median survival time 32 months versus 17 months, log-rank $P = 0.035$). Therefore, we suggested that delayed surgery could be conducted for patients with a cCR to neoadjuvant chemoradiation, and timely surgery should be arranged for patients with a non-cCR to neoadjuvant chemoradiation.

The main strength of this study is that it was the first to evaluate whether the delayed surgery was rational for patients with cCR to neoadjuvant chemoradiation. In addition, our study included over 200 patients with ESCC and was relatively reliable.

Several limitations of this study should be acknowledged. First, it was a retrospective single-centre study. Second, although the radiation dose was scheduled according to NCCN guidelines, it ranged from 40 to 50.4 Gy. This might be potential heterogeneity caused by personal experience.

CONCLUSIONS

Patients with a longer time interval between NACR and surgery had higher pathological complete response rates. For patients who achieve cCR to neoadjuvant chemoradiation, the time interval to surgery can be safely prolonged for at least 10 weeks. Delayed surgery in patients who have not recovered from NACR is applicable in clinical management. For patients who have non-cCR to neoadjuvant chemoradiation, delayed surgery is associated with poor survival, and surgery should be performed within 10 weeks after NACR.

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DISCLOSURES The authors declare that they have no conflict of interest.

ETHICAL APPROVAL This study was approved by the Institutional Review Board of West China Hospital, Sichuan University (2021-909), and the need for informed consent was waived for all patients. This study was retrospectively registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=169557), where the protocol can be found. The registration ID is ChiCTR2200059906.

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