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Original Article

Association between time interval from neoadjuvant chemoradiotherapy to surgery and complete histological tumor response in esophageal and gastroesophageal junction cancer: a national cohort study

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SUMMARY. **The optimal time interval from neoadjuvant therapy to surgery in the treatment of esophageal cancer is not known. The aim of this study was to investigate if a prolonged interval between completed neoadjuvant chemoradiotherapy and surgery was associated with improved histological response rates and survival in a population-based national register cohort. The population-based cohort study included patients treated with neoadjuvant chemoradiotherapy and esophagectomy due to cancer in the esophagus or gastroesophageal junction. Patients were divided into two groups based on the median time from completed neoadjuvant treatment to surgery. The primary outcome was complete histological response. Secondary outcomes were lymph node tumor response, postoperative complications, R0 resection rate, 90-day mortality, and overall survival. In total, 643 patients were included, 344 (54%) patients underwent surgery within 49 days, and 299 (47%) after 50 days or longer. The groups were similar concerning baseline characteristics except for a higher clinical tumor stage ($P = 0.009$) in the prolonged time to surgery group. There were no significant differences in complete histological response, R0 resection rate, postoperative complications, 90-day mortality, or overall survival. Adjusted odds ratio for ypT0 in the prolonged time to surgery group was 0.99 (95% confidence interval: 0.64–1.53). Complete histological response in the primary tumor (ypT0) was associated with significantly higher overall survival: adjusted hazard ratio: 0.55 (95% CI 0.41–0.76). If lymph node metastases were present in these patients, the survival was, however, significantly lower: adjusted hazard ratio for ypT0N1: 2.30 (95% CI 1.21–4.35). In this prospectively collected, nationwide cohort study of esophageal and junctional type 1 and 2 cancer patients, there were no associations between time to surgery and histological complete response, postoperative outcomes, or overall survival. The results suggest that it is safe for patients to postpone surgery at least 7 to 10 weeks after completed chemoradiotherapy, but no evidence was seen in favor of recommending a prolonged time to surgery after neoadjuvant chemoradiotherapy for esophageal cancer. A definitive answer to this question requires a randomized controlled trial of standard vs. prolonged time to surgery.**

KEY WORDS: **esophageal cancer, histological complete response, neoadjuvant chemoradiotherapy, postoperative complication, survival, timing of surgery.**

INTRODUCTION

Modern curative treatment for patients with advanced locoregional esophageal cancer consists of neoadjuvant chemoradiotherapy (nCRT), followed by surgery, or surgery with perioperative chemotherapy.[1] The interval between the last day of nCRT and surgery has historically been set to 4 to 6 weeks in clinical practice.[2–4] In the Netherlands, this practice has been changed based on observational results from the CROSS trial cohort, to surgery within 8 weeks of completed nCRT.[5]

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Patient status, tumor response after neoadjuvant treatment, and the consequences of local inflammation at the time of esophagectomy all affect surgical outcome.[6,7] These factors have the potential to evolve over time, which implies that the correct surgical timing is essential to optimize the outcome. Concerning rectal cancer, a published meta-analysis, including 13 studies with a total of 3,584 patients, investigated the effect of prolonged time to surgery (TTS) by comparing the standard of 6 to 8 weeks from completed nCRT to surgery, with longer time intervals. Longer TTS was associated with improved histological complete response rate, with similar survival and complication rates.[8] In principle, this lack of improved survival was unexpected since it has repeatedly been shown that complete eradication of tumor cells by nCRT is associated with improved esophageal cancer survival.[9,10]

Published studies on the relevance of TTS in esophageal cancer display varied results. Retrospective studies have found that prolonged TTS increases the probability of histological tumor response without affecting overall survival.[5,11–14] Two large register-based cohort studies reported increased histological complete response and improved pathological downstaging with prolonged TTS, but a reduced overall survival.[15,16] Other retrospective studies found none of these associations.[17–19] Concerning risk for postoperative complications, the results of previous studies are ambiguous.[5,6,17,20–22] A subsequent meta-analysis including five studies, with considerable heterogeneity, indicated a reduced overall survival in case of prolonged TTS but with unchanged rates of complete histological response and postoperative complications.[7] The aim of this study was to assess whether longer TTS after completed nCRT was associated with[1] increased complete histological response,[2] differences in postoperative complications and mortality, and[3] differences in overall survival, compared to standard TTS in a national register-based cohort.

METHODS

Data collection

Data were retrieved from the nationwide population-based register, the Swedish National Register for Esophageal and Gastric Cancer (NREV), between January 2006 and April 2017, with follow-up concerning survival to March 2018. Exposure and outcome data were prospectively registered and the enrolled patients were cross-matched to the National In-Patient Register and Cause of Death Register by each individual's unique personal identification numbers assigned to all Swedish residents.[23–25] All patients that underwent esophagectomy with curative intent due to cancer in the esophagus or gastroesophageal junction cancer, including Siewert types I and II (clinical tumor stage T1-T4 with any N stage), were included in the study.

The Swedish National Register for Esophageal and Gastric Cancer

The register was started in 2006, and to date more than 95% of patients with esophageal or gastric cancers diagnosed in Sweden have been registered. The register has a coverage of 95.5% of all incident gastric and esophageal cancers diagnosed in Sweden, and a recent validation study showed an overall accuracy of 91%.[26] Online data forms are used. The first form is reported at time of diagnosis, the second at surgery, and the third at the first postoperative follow-up. The register is monitored by regional cancer centers, and completion is certified by regular follow-ups. Baseline variables, measured at time of diagnosis, include tumor characteristics, age, sex, American Society of Anesthesiologists score (ASA score), and ECOG Performance Status. Postoperative morbidities are reported as surgical or nonsurgical complications.

Exposure

TTS was determined with the use of the Swedish inpatient register and NREV measuring the time from last day of nCRT to the day of surgery.[24,25] The patients were divided into two groups based on the median TTS after completed neoadjuvant treatment. The main nCRT regimens used for patients with adenocarcinoma or squamous cell carcinomas during 2006–2012 consisted of three cycles of cisplatin 100 mg/m^2 day 1, and 5-fluorouracil 750 mg/m^2/24 hours days 1 to 5, and concomitant radiotherapy in 2 Gy fractions with a total dose of 40 Gy. Since the publication of the CROSS trial in 2012, the standard regimen has been weekly carboplatin AUC 2 mg/mL/min and paclitaxel 50 mg/m^2, in combination with concomitant radiotherapy in 1.8 Gy fractions with a total dose of 41.4 Gy.[3]

Outcomes

The primary outcome was complete histological tumor response in the primary tumor (ypT0). Secondary outcomes included complete histological response in primary tumor and lymph nodes (ypT0N0), postoperative complications, R0 resection rate, 90-day mortality, and overall survival. All reported complications were included in the analyses. Postoperative surgical complications included:

1. Anastomotic leakage, defined as a clinically relevant leak and confirmed with CT scan with an oral water-soluble contrast medium or, in case of uncertainty, verified with endoscopy;
2. Conduit necrosis, defined as clinically significant ischemia with perforation or ulcer;

Table 1 Characteristics of patients treated with neoadjuvant chemoradiotherapy for cancer in the esophagus, by time to surgery

N (%)	Time to surgery ≤49 days	Time to surgery >49 days	*P*-value
Total	344 (53.5)	299(46.5)	—
Median days to surgery (IQR)	31 (28–42)	71 (58–91)	<0.001
Median months to follow-up (IQR)	59 (36–97)	48 (25–82)	0.016
Age in years, median (range)	64 (20–80)	65 (33–83)	0.255
Gender			
Female	57 (16.6)	50 (16.7)	0.959
Male	287 (83.4)	249 (83.3)	
Performance status†			0.832
0	223(66.0)	185 (63.8)	
1	106 (31.4)	96 (33.1)	
2	9 (2.7)	9 (3.1)	
Unknown	6	9	
ASA score‡			0.735
I	142 (42.0)	117 (39.7)	
II	174 (51.5)	155 (52.5)	
III	22 (6.5)	23 (7.8)	
Unknown	6	4	
Histological tumor type			0.582
Adenocarcinoma	256 (74.4)	211 (71.8)	
Squamous cell carcinoma	74 (21.5)	74 (24.8)	
Other	14 (4.1)	13 (4.4)	
Unknown	0	1	
Clinical T stage¶			0.009
T1	10 (3.2)	8 (2.9)	
T2	100 (31.6)	54 (19.4)	
T3	190 (59.9)	199(71.6)	
T4	17 (5.4)	17 (6.1)	
Unknown	27	21	
Clinical N stage††			0.210
N0	176 (52.1)	143 (48.3)	
N1	136 (40.2)	116 (39.2)	
N2	21 (6.2)	32 (10.8)	
N3	5 (1.5)	5 (1.7)	
Unknown	6	3	

†ECOG/WHO performance status score 0–5. ‡American Society of Anesthesiologists physical status classification. ¶Tumor stage (TNM) was assessed by endoscopy and computed tomography with optional use of endoscopic ultrasonography (EUS) and PET-CT. ††Clinical N stage was assessed by means of endoscopic ultrasound or FDG-PET-CT.

3. Bleeding, defined as a blood loss of more than 2 L or need for surgical reintervention;
4. Chylothorax, defined as significant when needing drainage for more than 7 days or when requiring surgical re-intervention; or
5. Recurrent laryngeal nerve paralysis, confirmed by an otolaryngologist.
6. Abdominal or thoracic abscesses were reported when the size was over 3 × 3 cm and verified radiographically or surgically.

Postoperative nonsurgical complications included cardiac arrhythmias requiring medical treatment, myocardial infarction, and cerebral embolism. Pulmonary embolism was defined as radiographically-confirmed emboli requiring treatment. Respiratory failure was defined as patients requiring invasive or noninvasive ventilator support. Pneumonia was defined by typical findings on chest x-ray combined with fever, cough and/or dyspnea. Infections not related to the operation field were also recorded. Septicemia was defined as body temperature above 38.3°C (101°F) or below 36°C (96.8°F) with a positive blood culture.

Mortality was calculated with data from the Cause of Death Register and presented as 90-day mortality, and overall mortality was calculated from the date of the surgery until death or censoring on March 11, 2018. The resection specimens, including primary tumor and all resected lymph nodes, were processed according to a standardized protocol. Overall survival was analyzed depending on TTS, and histological response was defined as ypT0, ypN0, ypT0N0, and ypT0N1.

Statistical methods

Multivariable logistic regression modeling, the chi-square test, and Fisher's exact test were used for binomial outcomes. The multivariable logistic regression model and Cox proportional hazard model were pre-specified, and included histological tumor type, clinical T stage, clinical N stage, age, gender, and baseline ECOG performance status. The categorizations of the variables are displayed in Table 1. The Cox proportional hazard model was used for the survival analyses. The proportional hazard assumptions were tested in all models using the Grambsch and Therneau test

Table 2 Effect of time to surgery on short-term surgical outcome after neoadjuvant chemoradiotherapy

n (%)	TTS ≤ 49 days	TTS > 49 days	*P*-value
Total	344 (53.5)	299 (46.5)	—
Surgical complications	106 (30.8)	86 (28.8)	0.571
Nonsurgical complication	83 (24.1)	91(30.4)	0.073
Anastomotic leak	36 (10.5)	34 (11.4)	0.713
Conduit necrosis	19 (5.5)	4 (1.3)	0.004
Postoperative bleeding	4 (1.2)	5 (1.7)	0.583
Thoracic duct injury	16 (4.7)	9 (3.0)	0.283
Abdominal abscess	2 (0.6)	4 (1.3)	0.320
Thoracic abscess	14 (4.1)	13 (4.4)	0.861
Recurrent laryngeal nerve paralysis	21 (6.1)	11 (3.7)	0.158
Pneumonia	33 (9.6)	39 (13.0)	0.166
Sepsis	16 (4.7)	27 (9.0)	0.027
Cardiovascular complication	14 (4.1)	15 (5.0)	0.564
Pulmonary emboli	6 (1.7)	11 (3.7)	0.127
Clavien-Dindo score			0.193
I	38 (26.8)	24 (18.9)	
II	45 (31.7)	35 (27.6)	
IIIa	25 (17.6)	21 (16.5)	
IIIb	22 (15.5)	22 (17.3)	
IVa	8 (5.6)	17 (13)	
IVb		2 (1.4)	3 (2.4)
V	2 (1.4)	5 (3.9)	
Unknown	202	172	
R0 resection	304/324 (93.8)	234/252 (92.9)	0.642
Number of resected lymph nodes, median (IQR)	15 (10–25)	18 (11–26)	0.010
Number of malignant lymph nodes, median (IQR)	0 (0–2)	0 (0–2)	1.0
Median length of hospital stay (IQR)	14 (10–23)	16 (11–24)	0.010

based on Schoenfeld residuals, which did not show any violations. For each outcome, we report the odds ratio (OR) and 95% confidence interval (CI) for those who had surgery with standard TTS (≤49 days) relative to those who had prolonged TTS (>49 days). All *P*-values were two-tailed, and 0.05 was considered statistically significant. Median TTS and interquartile range (IQR) are presented. Analyses were performed using STATA® version 13 software (StataCorp LP, College Station, Texas, USA). Approval for the study was granted by the Regional Research Ethics Committee, Stockholm (2013/596-31/3).

RESULTS

The total number of patients treated with nCRT followed by esophagectomy with curative intent was 643. Surgery with TTS ≤ 49 days was performed in 344 (53.5%) patients (standard TTS) and >49 days in 299 (46.5%) patients (prolonged TTS). Median TTS in the standard group was 38 days (IQR: 28–42) versus 71 days (IQR: 58–91) in the prolonged TTS group. Patients were followed for an average of 53 months (range 11–146). The prolonged TTS group had statistically significant higher clinical T-stage ($P = 0.009$, Table 1). There were no significant differences in age, gender, ASA scores, ECOG performance status, or N stage between the groups (Table 1).

Surgical complications were reported in 30.8% of the patients in the standard TTS group and in 28.8% of the patients with prolonged TTS ($P = 0.571$, Table 2). Anastomotic leaks were reported in 10.5% of the patients in the standard TTS group, versus 11.4% for prolonged TTS ($P = 0.713$). Conduit necrosis occurred in 5.5% in the standard TTS group versus 1.3% for prolonged TTS ($P = 0.004$). Nonsurgical complications were reported in 24.1% in the standard TTS group and in 30.4% in the prolonged TTS group ($P = 0.073$). Sepsis occurred in 4.7% versus 9.0% for standard versus prolonged TTS, respectively ($P = 0.027$, Table 2).

The 90-day mortality rate was 6% in both groups. The R0-resection rate was 93.8% in the standard TTS group and 92.9% in the prolonged TTS group. The median number of resected lymph nodes was 15 in the standard TTS group and 18 in the prolonged TTS group ($P = 0.010$, Table 2).

There was no association between TTS and complete histological response in the primary tumor (ypT0) or for complete histological response in primary tumor as well as lymph nodes (ypT0N0). Multivariable adjusted odds ratio in the prolonged TTS group was for ypT0: 0.99 (95% CI 0.64–1.53), ypN0: 1.14 (95% CI 0.79–1.66), and ypT0N0: 0.96 (95% CI 0.61–1.52), compared to standard TTS (Table 3). Subgroup analyses including only adenocarcinomas showed similar results with no association between TTS and histological tumor response (Table 3). There was no association between TTS and overall survival, adjusted hazard ratio: 0.99 (95% CI 0.79–1.24, Fig. 1). The effect of TTS on histological complete response was also analyzed with

Table 3 Effect of time to surgery on histological response and survival

	TTS ≤ 49 days	TTS > 49 days	*P*-value
ypT0	77 (24.3)	55 (23.3)	0.788
ypN0	185 (58.0)	153 (61.9)	0.342
ypT0N0	70 (22.5)	48 (20.7)	0.611
Unknown ypTNM	25	52	
90-day mortality	20 (6)	18 (6)	0.912
Multivariable regression model of time to surgery, histological tumor response, and 90-day mortality			
	Odds ratio (95% confidence interval)†		
ypT0	1.0 (reference)	0.99 (0.64–1.53)	0.955
ypN0	1.0 (reference)	1.14 (0.79–1.66)	0.482
ypT0N0	1.0 (reference)	0.96 (0.61–1.52)	0.866
90-day mortality	1.0 (reference)	0.96 (0.48–1.92)	0.911
Patients with adenocarcinoma			
ypT0	51 (21.7)	33 (19.3)	0.555
ypN0	125 (53.4)	106 (59.6)	0.214
ypT0N0	46 (20.1)	28 (16.7)	0.387
Unknown ypTNM	21	40	
Multivariable regression model of time to surgery and histological tumor response			
	Odds ratio (95% confidence interval)‡		
ypT0	1.0 (reference)	0.89 (0.52–1.52)	0.658
ypN0	1.0 (reference)	1.26 (0.82–1.94)	0.290
ypT0N0	1.0 (reference)	0.82 (0.46–1.46)	0.492

†Adjusted for histological tumor type, clinical T stage, clinical N stage, age, gender, and ECOG performance status. ‡Adjusted for clinical T stage, clinical N stage, age, gender, and ECOG performance status.

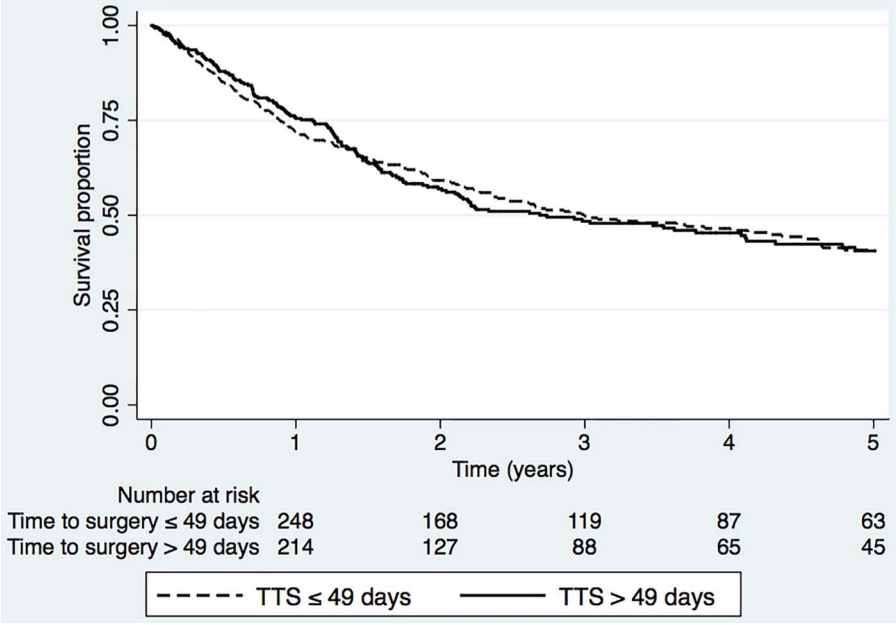

Fig. 1 Kaplan–Meier graph of overall survival after neoadjuvant chemoradiotherapy stratified by time to surgery.

TTS as a continuous variable without showing any significant association (data not shown).

Complete histological response in the primary tumor (ypT0) was associated with significantly higher overall survival, adjusted hazard ratio: 0.55 (95% CI 0.41–0.76). If lymph node metastases were present in these patients, the survival was, however, significantly lower: adjusted hazard ratio for ypT0N1: 2.30 (95% CI 1.21–4.35). Complete histological tumor response, defined as ypT0N0, was strongly associated with higher overall survival; adjusted hazard ratio 0.47 (95% CI 0.33–0.66, Table 4 Fig. 2).

DISCUSSION

This population-based cohort study investigated the relevance of time from completed nCRT to surgery in curatively intended treatment of esophageal and gastroesophageal junction cancer. Different TTS was not associated with histological tumor response, early

Table 4 Effect of time to surgery and histological response on overall survival

	Hazard ratio (95% confidence interval)	*P*-value
Time to surgery TTS > 49 days	0.99 (0.79–1.24)†	0.905
ypT0	0.55 (0.41–0.76)‡	<0.001
ypN0	0.38 (0.30–0.48)‡	<0.001
ypT0N0	0.47 (0.33–0.66)‡	<0.001
ypT0N1	2.30 (1.21–4.35)‡	0.011

†Adjusted for histological tumor type, clinical T stage, clinical N stage, age, gender, and ECOG performance status. ‡Adjusted for histological tumor type, age, gender, and ECOG performance status.

postoperative outcomes, or overall survival, regardless of histological tumor type. As expected, there was a strong association between complete histological tumor response, defined as ypT0N0, and higher overall survival. On the other hand, complete histological response in the primary tumor, in conjunction with ypN1, was associated with significantly lower survival.

Limitations of the current study include the non-randomized design and that information concerning the reason for the prolonged TTS was not available in the individual patient. Details about the administered oncological treatments were unfortunately not available in the register which is why the effects of different regimens and length of or adverse events during neoadjuvant treatment could not be evaluated. There may be some patient selection bias in our study, as TTS within 4 to 6 weeks was standard practice during the study period, so a prolonged TTS was due to either administrative reasons or patient-related factors. Hence, patients with poor physical status or adverse events during neoadjuvant treatment might be overrepresented in the prolonged TTS group, as well as patients who had to discontinue neoadjuvant treatment due to adverse events. However, there were no significant differences in baseline ASA-score or ECOG Performance Status. There was significantly higher clinical T-stage in the prolonged TTS group, which was included in the multivariable adjusted analyses. Selection bias might have camouflaged positive effects of prolonged TTS. Time to surgery was dichotomized based on median time (49 days), the same cut-off used in a previous French study.[21] A sensitivity analysis using TTS as a continuous variable did not change the results. The Clavien-Dindo scores for postoperative complications were introduced in the register in 2012, which decreases the sample size for analyses of this outcome. The definitions of the complications recorded in the NREV register do not, unfortunately, match the ECCG definitions,[27] which would improve the opportunity for international comparisons. However, all recorded definitions in the register have clear predefined definitions. Other strengths of the study include the population-based design including more than 95% of all patients with esophageal cancer in Sweden[26] and the complete follow-up concerning survival.

An association between TTS and histological tumor response, which has been demonstrated in some previous studies,[11–13,15,16] but not in

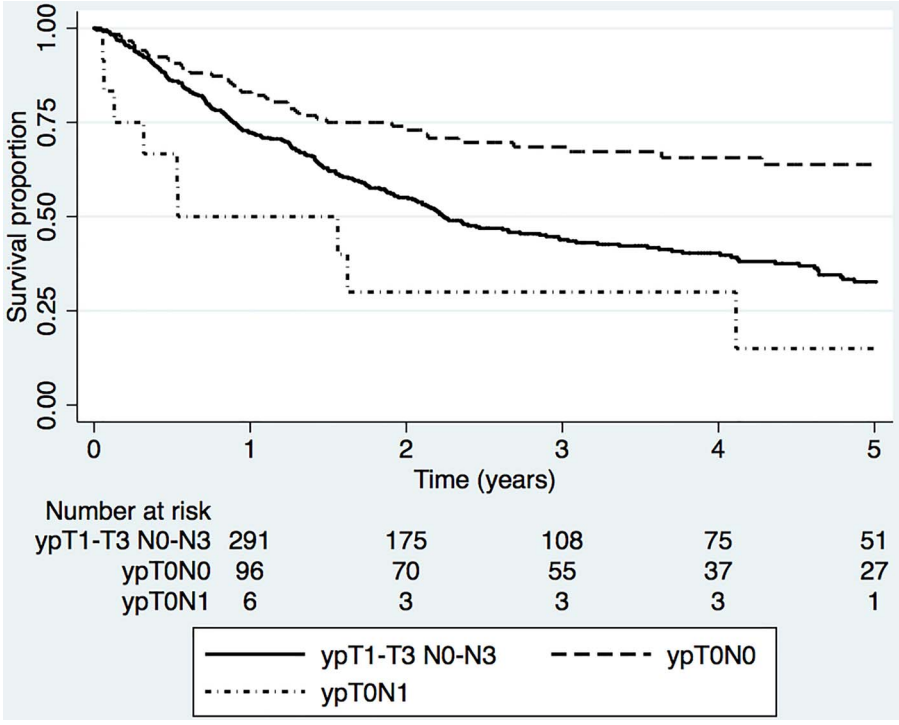

Fig. 2 Kaplan–Meier graph of overall survival after neoadjuvant chemoradiotherapy stratified by histological response.

others,[17,20,22] was not seen in the current study. We did find that the median number of resected lymph nodes was significantly higher in the prolonged TTS group, which indicates that surgery in the prolonged TTS group has at least the same quality as in the early TTS group. The study shows similar results as previous studies concerning the lack of difference in overall postoperative complications, and the fact that sepsis was less frequent in the standard TTS group and conduit necrosis was less frequent in the prolonged TTS group might well be a random finding. The findings of the current study are in agreement with the results from previous studies and a meta-analysis not showing an association between TTS and overall survival.[5,11–17,19–22,28]

A possible advantage with prolonged TTS is that patients who do not respond to the neoadjuvant treatment would have more time to be thoroughly evaluated, and at signs of progressive distant metastatic disease, noneffective and detrimental surgical resection could be aborted in place of suitable palliative care. This possible benefit could not be addressed in the current or in previous observational studies.

Complete histological primary tumor response, ypT0, was associated with significantly increased overall survival, a fact that has been demonstrated in numerous previous studies.[2,9,10,29,30] Interestingly, this group by definition includes patients with pathological lymph node involvement. Pathologic tumor stage ypT0 and ypN1-N3 was associated with significantly decreased survival compared to all other patients. Complete histological tumor response, when defined as ypT0N0, was strongly associated with increased survival and perhaps should be considered gold standard in treatment response evaluation. Lymph node status, regardless of histological tumor response, has previously been demonstrated to be the strongest predictor for prognosis after neoadjuvant chemotherapy.[31]

The outcomes of randomized controlled studies advocating the value of neoadjuvant treatment have had a significant impact on the management of esophagogastric cancer patients in the Western world.[1,3,32] However, when applying the trial regimens in daily clinical practice, the benefits may not be as clear as in the trials. This problem of generalizability of trial results has been shown for several gastrointestinal cancers.[33,34] Obviously, the TTS after neoadjuvant therapy remains controversial, and there are a variety of factors that may be of importance. Nevertheless, a longer TTS allows for more recovery time after the neoadjuvant treatment which might improve baseline performance status by giving the patients an opportunity to improve their nutritional status and allow the side effects of radiotherapy to subside.

In conclusion, this study showed, in a prospectively collected nationwide cohort of esophageal and junctional type 1 and 2 cancer patients, no association between TTS and complete histological tumor response, postoperative outcomes, or overall survival, after curatively intended nCRT. The results suggest that it is safe for patients to wait at least 7 to 10 weeks after completed nCRT for surgery, but no evidence was seen in favor of recommending a prolonged TTS after nCRT for esophageal cancer. A definitive answer to this question requires a randomized controlled trial of standard versus prolonged TTS.

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