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# Impact of interval timing to surgery on tumor response after neoadjuvant treatment for gastric cancer

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## ABSTRACT

**Introduction:** neoadjuvant chemotherapy (NACT) followed by radical surgery is the optimal approach for locally advanced gastric cancer (GC). Interval timing to surgery after NACT in GC is controversial. The aim of this study was to evaluate the impact of NACT interval time on tumor response and overall survival.

**Material and methods:** a retrospective analysis from a prospective database was performed at a single referral tertiary hospital, from January 2010 to October 2018. Patients were assigned to three groups according to the surgical interval time after NACT: < 4 weeks, 4-6 weeks and > 6 weeks. Univariate and multivariable analyses were performed in order to clarify the impact of NACT on post-neoadjuvant pathological complete response rate (ypCR), downstaging (DS) and overall survival (OS).

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**Results:** of the 60 patients analyzed, 18 patients (30%) had an interval time to surgery < 4 weeks, 26 (43.3%) between 4-6 weeks and 16 (26.7%) > 6 weeks. Two patients (3%) had achieved ypCR and 37 patients (62%) had achieved DS. There were no differences in DS rates among the interval time groups (p: 0.66). According to the multivariate analysis, only poorly differentiated carcinoma was significantly related to lower DS rates (p: 0.04). Cox regression analysis showed that the NACT interval time had no impact on OS. According to the multivariate analysis, > 25 lymph node harvested (HR: 0.35) and female sex (HR: 5.67) were OS independent predictors.

**Conclusions:** the NACT interval time prior gastrectomy for locally advanced GC is not associated with ypCR or DS and has no impact on overall survival.

**Keywords:** Impact. Timing of surgery. Neoadjuvant chemotherapy. Gastric cancer. Tumor response. Downstaging. Overall survival.

## INTRODUCTION

Neoadjuvant chemotherapy (NACT) followed by radical surgery is the optimal approach for locally advanced gastric cancer (GC) (1,2). However, the five-year survival rates remain poor (< 40%), despite the increased use of perioperative chemotherapy.

The most important aim of NACT is the possibility of post-neoadjuvant pathologic complete response (ypCR) or even tumor downstaging (DS). It has been shown in bladder and rectal cancer (3,4) that patients with a ypCR might achieve a better overall survival (OS) and disease free survival (DFS). Nevertheless, there is still no agreement in GC about whether ypCR or DS is associated with OS improvement. Although the relationship between ypCR and tumor response with better survival outcomes has been reported in a few studies (5-8), other studies have published the opposite results (9,10).

Furthermore, the impact of the interval timing after NACT on ypCR and OS has been tested in rectal and esophageal cancer. However, the optimal time between NACT and surgery and its relation with OS has scarcely been investigated in GC. Some trials have proposed an interval of 4-6 weeks (11,12), but this has never been validated. Recently, Liu et al. have suggested that an interval time after NACT of > 6 weeks had a positive

impact on ypCR compared with either 4-6 weeks or < 4 weeks (13), but these intervals did not have an impact on either OS or DFS. Although several authors have reported a positive impact from delaying the interval time after NACT on ypCR rate and short-term outcomes in rectal cancer (14,15), the results in esophageal or even GC are controversial (16-18).

The main objective of this study was to evaluate the impact of the interval time after NACT on tumor response (ypCR/DS). The second endpoint was to assess the association between optimal interval time and OS. Finally, whether a longer interval time (> 6 weeks) than is currently accepted (4-6 weeks) is safe and its association with oncological outcomes was also determined.

## MATERIAL AND METHODS

### Patient selection criteria

A retrospective analysis from a prospective database was performed at a single referral tertiary hospital from January 2010 to October 2018. A total of 349 GC patients were initially recruited during this period. The main inclusion criteria were: a) GC adenocarcinoma found by histopathology analysis; b) patients under 85 years with ECOG 0-1; c) locally advanced GC (T3-4, N0-3, and M0) with complete NACT prior to surgery; and d) patients with complete clinical pathological information including surgical and neoadjuvant, perioperative and surveillance data.

Exclusion criteria were: a) patients older than 85 years or under 85 years ECOG > 1; b) patients with renal, liver or hematological failure; c) patients who received neoadjuvant chemoradiotherapy; and d) patients with peritoneal carcinomatosis. From 322 patients, only 60 were finally included in the study. The inclusion of patients to a NACT program in GC surgery at our institution has been gradual until its complete implementation during the last six years. The flow diagram of patient inclusion is shown in figure 1.

All patients were staged and treated according to Japanese gastric cancer guidelines and the 7$^{th}$ AJCC edition (19,20). Before neoadjuvant treatment, the preoperative work-up of patients included an endoscopic ultrasound (EUS), body computed tomography (CT) and complete oral endoscopy in order to assess the correct clinical

stage.

**Neoadjuvant chemotherapy, surgery and histopathology analysis**

Neoadjuvant treatment was decided by a multidisciplinary committee. ECF (intravenous epirubicin 50 mg/m$^2$ and cisplatin 60 mg/m$^2$ every three weeks, with continuous infusion of 5-FU 200 mg/m$^2$ per day), EOx (intravenous epirubicin 50 mg/m$^2$ day 1, oxaliplatin 130 mg/m$^2$ day 1 and oral capecitabine twice-daily dose of 1,000 mg/m$^2$ for two weeks) and FLOT (intravenous docetaxel 60 mg/m$^2$, oxaliplatin 85 mg/m$^2$, leucovorin 200 mg/m$^2$ and 5-fluoracil 2,600 mg/m$^2$, all given on day 1 and administered every two weeks) were the main chemotherapy regimens administered.

Tumor regression was evaluated according to RECIST 1.1 with a CT scan two weeks after chemotherapy. Patients without metastasis underwent a gastrectomy according to the Japanese gastric cancer guidelines. Patients were assigned to three groups according to the surgical interval time after chemotherapy neoadjuvant treatment: < 4 weeks, 4-6 weeks and > 6 weeks.

Patients with post-neoadjuvant therapy pathological (yp) T0N0M0 were defined as having an ypCR. Downstaging (DS) was determined when a decrease of T and/or N stage was found according to the preoperative work-up.

**Main and secondary endpoints**

The main objective of this study was to evaluate the impact of the interval time after NACT on tumor response (ypCR/DS). The second endpoint was to assess the association between optimal interval time and OS. Finally, whether a longer interval time (> 6 weeks) than the currently accepted (4-6 weeks) is safe and its association with oncological outcomes was also assessed.

**Statistical analysis**

Statistical analysis was performed with the SPSS version 23.0 software (SPSS Inc., Chicago, IL). The Chi-squared test and Fisher's test were used for categorical variables. The distribution of continuous data was tested, normally distributed data are presented as the mean and 95% confidence interval (CI) and differences between

groups were tested using the unpaired t test. Logistic regression was used to perform multivariable analysis where variables with a p-value > 0.2 were included. Overall survival was calculated with the Kaplan-Meier method and the log-rank test was used to analyze and compare survival curves in different interval time groups. A p-value of 0.05 was considered as statistically significant.

**RESULTS**

Among 60 patients analyzed, 32 patients (53.3%) were male, with a male:female ratio of 1.14/1 and the median age was 68 years (range, 41-81). Eighteen patients (30%) had an interval time to surgery < 4 weeks, 26 (43.3%) patients between 4-6 weeks and 16 (26.7%) > 6 weeks. Patients' baseline data, tumor characteristics, surgical related factors and surgical complications are shown in table 1. No differences were found with regard to age, sex, neoadjuvant chemotherapy treatment, tumor characteristics and histopathological findings among the three groups of interval time to surgery (< 4, 4-6 and > 6 weeks). Only the open approach procedure was more likely in the > 6 weeks group (81.3% *vs* 18.8%; p: 0.04). There were no other differences between any other surgical characteristics studied among the three groups.

**Impact of NACT-surgery interval time on ypCR and downstaging**

Two patients (3%) achieved ypCR. No patient surgical or tumor characteristics analyzed were statistically associated with ypCR. Thirty-seven patients (61.7%) achieved DS. Among the DS group, eleven patients (29.7%) were included in the < 4 weeks group, 15 patients (40.5%) in the 4-6 weeks group and eleven patients (29.7%) in the > 6 weeks group. No differences were found in DS rates among the interval time groups (p: 0.66). According to the univariate analysis, the type of neoadjuvant chemotherapy (EOx) (p: 0.02), clinical node status (N0 and N3) (p: 0.01 and p: 0.01, respectively), well differentiated carcinoma (p: 0.01) and resection status (R0) (p < 0.01) were significantly associated with DS status. Furthermore, poorly differentiated carcinoma was significantly associated with lower DS rates (p < 0.01). According to the multivariate analysis, only poorly differentiated carcinoma was significantly related to lower DS rates (p: 0.04) (Table 2).

**Impact of NACT-surgery interval time on OS**

Kaplan-Meier analysis for OS is shown in figure 2. The median OS was 49.94 months (range, 40.25-59.64 months). There were no significant differences among the three interval time groups in terms of survival outcome (p = 0.14). DS status was not significantly associated with OS. Female sex (p: 0.04) and > 25 lymph node harvested (p: 0.03) were significant independent OS factors (Table 3).

**DISCUSSION**

Although prognosis in GC remains poor, improved OS and ypCR rates have been reported after NACT following gastrectomy in some studies. Cunningham et al. reported a high tumor response after NACT with ECF and improved five-year OS (36% in the NACT group *vs* 23% for surgery alone) (11). However, this study was highly criticized due to the high rate of gastroesophageal junction tumors included, the poor quality of surgical technique and because only 42% of the included patients finished NACT treatment (20). Similar results were reported by Ychou et al., with a five-year OS improvement of 14% in the NACT group with cisplatin and 5-FU (21).

A meta-analysis by Xiong et al. found survival improvements and higher R0 rates in NACT groups, although there were no differences among different types of NACT (22). However, Al-Batran et al. more recently reported higher ypCR rates with FLOT *vs* ECF (16% *vs* 8%, respectively) in a phase II/III FLOT 4 trial (23). Similar results were found by the same group (24), the FLOT group had a 15-month improvement in five-year OS over the ECF group (50 months *vs* 35 months, respectively). Higher resectability rates were also achieved with NACT compared to surgery alone (12). In our clinical practice, we mainly use ECF as an NACT regimen before surgery. However, since the publication of Al-Batran et al., we have changed the preoperative treatment and nowadays the scheme with FLOT is the NACT regimen used in patients with GC.

Although the impact of interval time after NACT on tumor response and survival has been clearly proven in rectal and esophageal cancer, the optimal interval time after NACT and its relation with survival has scarcely been studied in GC. Some trials have proposed an interval of 4-6 weeks (12,20), but this has never been validated. Recently,

Liu et al. suggested that an interval time after NACT of > 6 weeks had a positive impact on ypCR compared with either 4-6 weeks or < 4 weeks (13). Preliminary previous internal research findings showed no differences in OS (log-rank: 0.52), clinical and pathological response between the < 6 weeks and > 6 weeks groups. In fact, ypCR was 3.2% *vs* 3.7% respectively (p = 0.923) and DS was 56.25% *vs* 67.85%, in favor of the > 6 weeks group, without statistically significant differences (p = 0.356). Thus, we have established three groups of patients according to Liu et al. (13) in order to have similar groups and to compare them with previously published studies. In any case, these intervals did not have an impact on either OS or DFS.

Regarding the main objective of this study, we wanted to evaluate the impact of the interval time after NACT on tumor response (ypCR/DS). NACT tumor response could be assessed by the possibility of post-neoadjuvant pathologic complete response (ypCR) or even a tumor downstaging (DS), which is more frequently observed in GC. Although several studies have reported wide intervals of ypCR, from 8% to 22% (13,23,24), only two patients (3%) in our series achieved a ypCR; one in the < 4 weeks group and one in the > 6 weeks group. Due to the low number of patients with ypCR in our study, an impact of the interval time after NACT on ypCR was not found. Furthermore, with regard to a partial response, 37 patients (61.7%) achieved DS but there were no differences in DS rates among the interval time groups (p: 0.66). In relation to tumor differentiation, the univariate analysis agreed with previous studies, which showed that the more differentiated tumors had a higher pathology response rate. However, in the multivariate analysis, only poorly differentiated carcinoma was statistically significantly related to lower DS rates (p: 0.04).

The second endpoint was to assess the association between optimal interval time after NACT and OS. Becker et al. found a complete response or subtotal regression in 20% and partial tumor regression (ranged from 10 to 50%) in 25% of the patients. Nearly half of these patients had a partial or total response to NACT. Tumor regression was a prognosis factor of survival outcome in GC in the Becker study (8). Other studies found similar tumor regression rates (22%), which was related to better survival outcomes (25,26). In our study, Cox regression analysis showed that there were no significant differences among the three interval time groups with regard to survival outcomes.

Similar results were found by Liu et al. in GC; better OS outcomes were not observed, despite higher ypCR rates in the longer interval time group (13).

Increased OS times were found in esophageal cancer by Meredith et al., with a five-year OS increase of 30% after NACT when ypCR was achieved (27). Similar results were found in rectal cancer, where five-year OS rates were nearly 100% when ypCR was achieved (4,28). ypCR might be the goal in GC after NACT, as in others gastrointestinal tumors. However, the survival impact factor of ypCR was not assessed in our study due to the low sample size and low ypCR incidence. According to the multivariate analysis, only > 25 lymph node harvested (HR: 0.35) and female sex (HR: 5.67) were OS independent predictors.

Different groups, especially in rectal and esophageal cancer, have studied the impact of interval time to surgery after NACT. Most of these studies recommended extending the interval time after NACT to more than 4-6 weeks. In rectal cancer, Al Shukhni et al. reported higher ypCR rates by increasing interval times to more than 6-8 weeks in contrast to the classically accepted four weeks (29). These results were similar to the findings by François et al., who reported higher ypCR and DS rates by increasing the interval time to 6-9 weeks (14). The same results were published by Hungtinton and Tran, who found a maximum response at eight weeks (15,30), although Lorimer et al. found higher ypCR rates (22%) beyond eight weeks (31). Nevertheless, García Aguilar et al., from MSKCC, reported that a longer interval time (6-8 weeks) was safe, but without higher tumor response (32). In esophageal cancer, Lee et al. found higher ypCR rates by increasing the interval time to more than seven weeks (12% to 18%), although it was not related to higher survival rates (16). These results were similar to those of the study by Kim et al., where no differences were found in ypCR rates, OS and morbidity, neither in the > 8 weeks group nor in the > 12 weeks group (33). Tessier et al. (34) did not find any differences in their study either. However, the impact of extending the interval time to more than six weeks in GC remains unclear and has never been proven.

On the other hand, the interval time to surgery value is unclear when regimens with only neoadjuvant chemotherapy (without radiotherapy) are used. The benefit of NACT has also been proven in bladder cancer (3) and pancreatic cancer (35), although the

impact of longer interval times has not been assessed. Yi Liu et al. (13) found that interval time (> 6 weeks) was related to higher odds of ypCR, but their findings did not have an impact on survival. These results were concordant with our findings. We did not find an increase in tumor response (DS) rates with a longer interval time (> 6 weeks) and there was no impact on OS among the three interval time groups. The type of NACT was not associated with different tumor response. According to our findings, waiting longer from NACT to surgery might be safe for the long-term outcome. However, there is no global consensus about the interval time following NACT in gastric cancer.

There were some limitations in our study. Its retrospective nature might produce some bias and a shorter follow-up time could affect the results. The main limitation was the small sample size to assess ypCR incidence properly and its associated bias. A multi-center randomized control study is required to validate our results and to evaluate the proper time to surgery after NACT.

To sum up, the NACT interval time after gastrectomy for locally advanced GC is not associated with ypCR or DS and has no impact on overall survival. A prolonged interval time > 6 weeks was not associated with increased tumor response or OS, but it is safe in patients who need a longer recovery period form NACT. Poor differentiated carcinoma was related to worse tumor response and lower DS rate after NACT. Patients with > 25 lymph nodes harvested have better OS outcomes.

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**Table 1. Demographic and tumor characteristics according to neoadjuvant chemotherapy, ypCR and DS status. Univariate analysis**

| | *< 4 w* | *4-6 w* | *< 6 w* | *p* | *No ypCR* | *ypCR* | *p* | *No DS* | *DS* | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Age (year) mean | 65.56 | 65.69 | 66.75 | 0.69 | 66.05 | 62.50 | 0.48 | 65.65 | 66.11 | 0.71 |
| Sex | | | | 0.32 | | | 0.07 | | | 0.08 |
| Male | 7 (38.9) | 16 (61.5) | 9 (56.3) | | 32 (55.2) | 0 (0) | | 9 (39.1) | 23 (62.2) | |
| Female | 11 (62.1) | 10 (38.5) | 7 (43.8) | | 26 (44.8) | 2 (100) | | 14 (60.9) | 14 (37.8) | |
| NACT | | | | 0.39 | | | 0.31 | | | *0.02* |
| ECF | 6 (33.3) | 11 (42.3) | 6 (37.5) | | 22 (37.9) | 1 (50) | | 8 (34.8) | 15 (40.5) | 0.65 |
| EOx | 2 (11.1) | 2 (7.7) | 3 (18.8) | | 6 (10.3) | 1 (50) | | 0 (0) | 7 (18.9) | *0.02* |
| FLOT | 7 (38.9) | 10 (38.5) | 2 (12.5) | | 19 (32.8) | 0 (0) | | 8 (34.8) | 11 (29.7) | 0.68 |
| Other | 3 (16.7) | 3 (11.5) | 5 (31.3) | | 11 (19) | 0 (0) | | 7 (30.4) | 4 (10.8) | 0.06 |
| ASA grade | | | | 0.06 | | | 0.52 | | | 0.41 |
| I | 1 (5.6) | 3 (11.5) | 0 (0) | | 4 (6.9) | 0 (0) | | 2 (8.7) | 2 (5.4) | |
| II | 13 (72.2) | 17 (65.4) | 7 (43.8) | | 36 (62.1) | 1 (50) | | 15 (65.2) | 22 (59.5) | |
| III | 4 (22.2) | 6 (23.1) | 9 (56.3) | | 18 (31) | 1 (50) | | 6 (26.1) | 13 (35.1) | |
| Tumor location | | | | 0.46 | | | 0.11 | | | 0.43 |
| EG junction | 3 (16.7) | 5 (19.2) | 2 (12.5) | | 8 (13.8) | 2 (100) | | 3 (13) | 7 (18.9) | |
| Fundus | 0 (0) | 2 (7.7) | 1 (6.3) | | 3 (5.2) | 0 (0) | | 0 (0) | 3 (8.1) | |
| Body | 8 (44.4) | 7 (26.9) | 8 (50) | | 23 (39.7) | 0 (0) | | 9 (39.1) | 14 (37.8) | |
| Antrum | 7 (38.9) | 10 (38.5) | 5 (31.3) | | 22 (37.9) | 0 (0) | | 10 (43.5) | 12 (32.4) | |
| Pylorus | 0 (0) | 2 (7.7) | 0 (0) | | 2 (3.4) | 0 (0) | | 1 (4.3) | 1 (2.7) | |
| Clinical T | | | | 0.32 | | | 0.75 | | | 0.39 |

w: weeks; ypCR: post-neoadjuvant pathologic complete response; DS: downstaging; NACT: neoadjuvant chemotherapy; ASA: American Society of Anesthesiologists; R status: resection status; LN harvest: lymph node harvest.

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**Table 2. Multivariate analysis. Independent predictors of downstaging**

| *Factor* | *HR* | *CI (95%)* | *p value* |
|---|---|---|---|
| Sex | 1.43 | 0.28-7.26 | 0.66 |
| Tumor differentiation | | | |
| Well differentiated | 2.66 | 0.14-10.65 | 0.08 |
| Poor differentiated | *0.17* | *0.03-0.92* | *0.04* |
| NACT | | | |
| EOx | 1.3 | 0.72-9.48 | 0.10 |
| Other | 3.24 | 0.40-8.45 | 0.26 |
| Clinical N | | | |
| cN0 | 2.10 | 0.34-7.96 | 0.42 |
| cN2 | 0.09 | 0.01-1.32 | 0.07 |
| cN3 | 0.31 | 0.10-2.45 | 0.20 |

NACT: neoadjuvant chemotherapy.

**Table 3. Multivariate analysis. Overall survival**

| | *Overall survival* | | |
|---|---|---|---|
| | *p value* | *HR* | *CI (95%)* |
| Female sex | *0.02* | 5.67 | 1.28-12.53 |
| NACT | | | |
| ECF | 0.48 | 1.27 | 0.32-5.68 |
| EOx | 0.45 | 1.52 | 0.24-6.76 |
| FLOT | 0.16 | 0.16 | 0.01-2.07 |
| Other | 0.22 | 0.43 | 0.25-3.29 |
| Tumor location | 0.36 | 0.69 | 0.31-1.51 |
| Clinical T | 0.16 | 2.30 | 0.70-7.52 |
| Gastrectomy | 0.58 | 1.75 | 0.23-9.03 |
| Interval time | | | |
| < 4 w | 0.64 | 1.26 | 0.45-3.51 |
| 4-6 w | 0.16 | 0.43 | 0.13-1.39 |
| > 6 w | 0.52 | 1.35 | 0.53-3.40 |
| Clinical N | 0.08 | 3.60 | 0.40-10.03 |
| Differentiation | | | |
| Well | 0.15 | 0.29 | 0.54-1.59 |
| Moderate | 0.12 | 0.22 | 0.03-1.48 |
| Poor | 0.75 | 1.15 | 0.46-2.83 |
| LN harvest | | | |

| | | *Overall survival* | |
|---|---|---|---|
| < 15 | 0.14 | 2.33 | 0.73-7.38 |
| 15-25 | 0.06 | 2.78 | 0.99-7.75 |
| > 25 | *0.02* | 0.35 | 0.14-0.83 |
| ypCR | 0.63 | 1.65 | 0.20-13.10 |
| DS | 0.87 | 0.93 | 0.37-2.33 |

w: weeks; ypCR: post neoadjuvant pathologic complete response; DS: downstaging; NACT: neoadjuvant chemotherapy; LN harvest: lymph node harvest.

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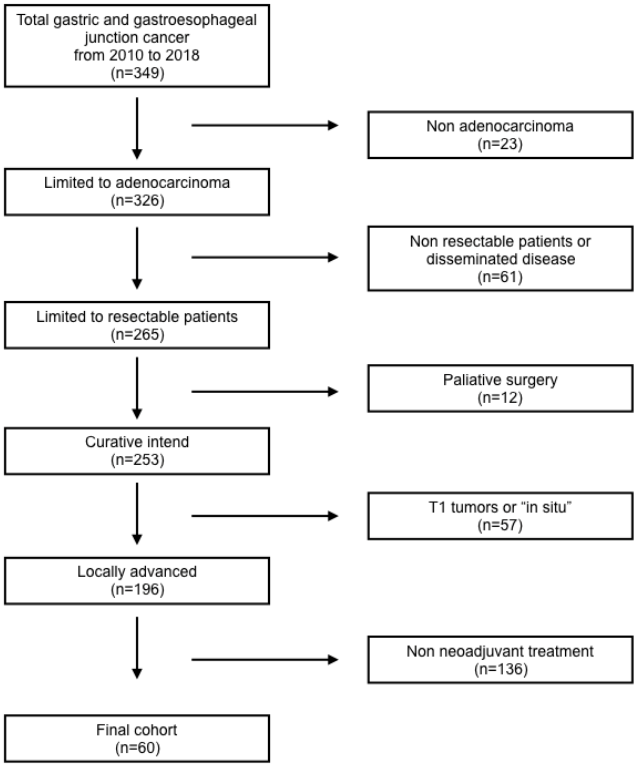


Fig. 1. Flowchart of patient selection.

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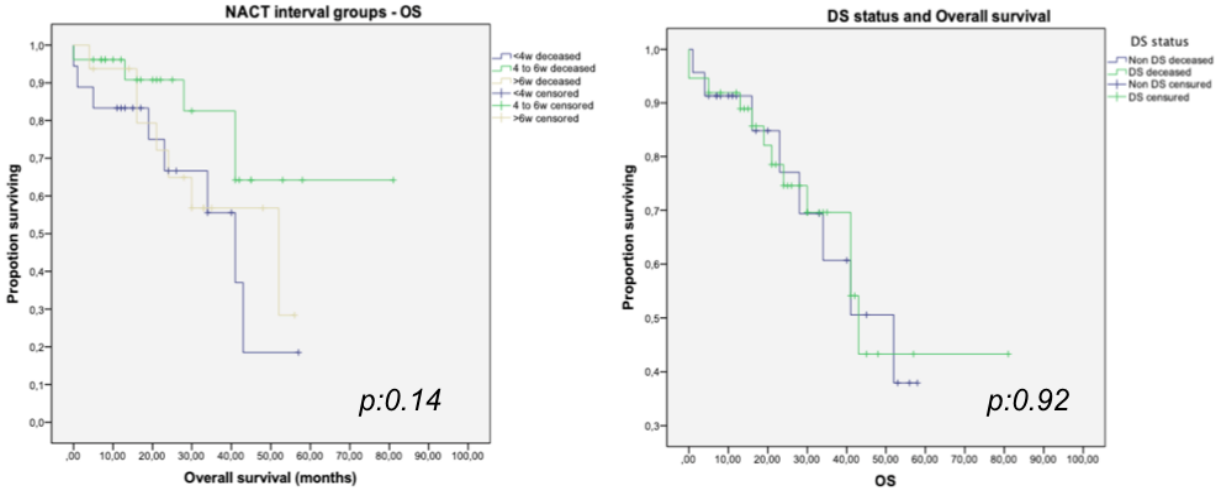


Fig. 2. A. NACT interval timing groups: overall survival (log-rank p = 0.14). B. Downstaging status: overall survival (log-rank p = 0.92).