Impact of Delay in Adjuvant Chemoradiation on Survival in Resected Gastric Cancer

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Research Article

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Abstract

Background

Adjuvant chemo(radio)therapy is known to improve survival in resected gastric cancer. However, there is scant data on the effect of delay in start of adjuvant treatment (AT) after surgery, and guidelines regarding optimal timing are mostly empirical.

Methods

In this ambispective analysis, we evaluated the survival outcome of patients who underwent upfront curative intent radical gastrectomy followed by AT at our center from 2002 through 2019. Cox proportional hazards model was used to identify predictors of recurrence-free survival (RFS) and overall survival (OS).

Results

Two-hundred and thirty patients (median age 53 years) with stage I-III carcinoma stomach were included. Seventy-six percent patients underwent D2 lymphadenectomy; 12% received adjuvant chemotherapy alone while 88% received chemoradiotherapy. AT was initiated at a median 42 days after surgery; 17% started within 4 weeks, 55% between 4–8 weeks, and 28% after 8 weeks. Five-year RFS and OS for full cohort were 42.3±4.2% and 63.2±4.4%, respectively. On multivariate analysis, disease stage, ECOG performance status and time to AT emerged as significant predictors of RFS and OS while extent of lymphadenectomy, number of resected lymph nodes and margin positivity did not. Initiation of AT after 8 weeks was associated with significantly worse 5-year RFS (HR 2.28; 95% CI, 1.29–4.04; p=0.005) and OS (HR 2.65; 95% CI, 1.27–5.52; p=0.010).

Conclusions

Delaying AT beyond 8 weeks after radical gastrectomy may be detrimental to disease recurrence and survival in patients with gastric cancer. If patients have adequately recovered, AT should preferably be initiated within 8 weeks of surgery.

Highlights

- Though adjuvant chemo(radio)therapy is standard of care for early gastric cancer, convalescence from gastrointestinal surgery is often prolonged, and little is known about the optimal timing of adjuvant treatment.
- In this ambispective study, we found that delaying adjuvant treatment beyond 8 weeks of radical gastrectomy was associated with a significantly higher risk for disease recurrence and death.
- The results provide a timeframe beyond which there is significant loss of efficacy, and oncologists should strive to start adjuvant therapy within this window.

- Eastern cooperative oncology group performance status also independently predicts for disease recurrence and survival.

Background

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer mortality globally, with more than one million new cases and approximately 769,000 deaths worldwide in 2020 (1). Surgical resection is the primary curative modality for invasive gastric cancer, but surgery alone is insufficient in a large proportion. Most patients undergoing gastrectomy for stage II/III gastric cancer have locoregional or distant relapse, and long-term survival after surgery alone is poor (2,3). Hence, perioperative and adjuvant treatment modalities have been used to prevent disease recurrence and improve outcomes. Multiple meta-analyses of randomized trials have confirmed that when compared with gastrectomy alone, administration of adjuvant chemotherapy, radiotherapy and combined chemoradiotherapy approaches significantly improve patient survival, with the latter being the most beneficial (4,5).

Though the impact of adjuvant chemotherapy and radiation on patient outcomes is well-established, there is scant data to guide the optimal timing of initiation of adjuvant treatment (AT) after surgery. The underlying principle of adjuvant treatment is to eradicate any residual micrometastatic disease after resection of the primary tumor. Animal model studies have demonstrated that surgical removal of a tumor leads to elaboration of a serum growth factor that accelerates the growth of residual cells within 24 hours, with measurable tumor growth within a week (6,7). Soon after surgery, the residual tumor volume is at its nadir, and it is at this point that a high proportion of tumor cells are in replicative phase (8). It stands to reason that institution of adjuvant therapy while most cells are in a susceptible phase would maximize the chances of disease eradication. Hence, most gastric cancer trials prefer initiation of AT within 4-8 weeks of gastrectomy, but the range has been widely variable. For instance, the landmark INT-0116 trial excluded patients if they were not registered and randomized within 20 – 40 days after surgery, and commenced therapy within further 7 days (9). In contrast, the CALGB 80101 (Alliance) trial allowed patient randomization up to 84 days after surgery (10). There is little high-quality evidence to inform the optimal timing of adjuvant chemoradiotherapy, and this range appears to be mostly empirical. Moreover, in routine clinical management of gastrointestinal cancers, AT is frequently delayed due to inadequate recovery from surgery, general patient debility, and surgical complications including wound infections and anastomotic leaks. Late initiation of AT has been associated with inferior survival in patients with colorectal cancer and breast cancer (11–13). Some retrospective studies have evaluated the impact of timing of AT on survival in gastric cancer, but the results have been inconsistent (14,15).

We conducted this study to analyze if a delay in initiation of adjuvant chemotherapy or chemoradiotherapy following upfront curative intent gastrectomy affects disease control and survival in patients with stomach cancer.

Methods

Study design and participants

This was an ambispective cohort study in which we collected data on all patients who underwent upfront curative intent surgical resection for stages I-III stomach cancer between January 1, 2002 and December 31, 2019 at All India Institute of Medical Sciences, New Delhi, India. Surgical procedures included radical total or subtotal gastrectomy with adequate lymph node dissection. Adjuvant chemotherapy and radiotherapy were started at the discretion of treating physicians after review in multidisciplinary tumor board meeting. Patients who received neoadjuvant chemotherapy or those who underwent palliative intent gastrectomy (including intra-operatively detected advanced disease) were excluded, as were patients with non-adenocarcinoma histology. The study protocol was approved by the institutional ethics committee.

Data collection

We accessed patient treatment records to extract the requisite data, which included patient demographics, performance status at diagnosis, extent of surgical resection including lymph node dissection, tumor location, pathological stage of tumor (per American Joint Committee on Cancer, 7^{th} edition), adjuvant treatment details and time to start of adjuvant chemoradiotherapy. Patients were categorized into two groups based on the interval between gastrectomy and AT initiation – early group (within 8 weeks) and delayed group (after 8 weeks); data regarding course of treatment and associated toxicity was also collected. Patients were followed up until recurrence or death from any cause, and those without an event were censored at the last follow-up date or April 20, 2021, as applicable. Patients with significant missing data were excluded.

Study outcomes and statistical analysis

Primary endpoint of the study was recurrence-free survival (RFS), which was defined as the time from surgery to first documented disease recurrence or death from any cause. Secondary endpoint was overall survival (OS), defined as time from surgery to death from any cause. Descriptive statistics are reported as mean (± standard deviation) or median (interquartile range, IQR). Time-to-event endpoint analysis was done using Kaplan-Meier method and differences between survival curves were examined using log-rank test. Cox proportional hazards model was used to evaluate the impact of AT timing and other variables on survival outcomes. Factors with p-values <0.2 in univariate analysis were included in multivariate analysis to identify variables independently predictive of RFS and OS. All tests were two-sided, and p-value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 13.0 (StataCorp, Texas).

Results

During the study period, 1378 patients were treated for stomach cancer at our centre; of these, 315 patients underwent upfront curative intent gastrectomy and were planned for adjuvant treatment. Sixty-three patients went to other centres for AT, while 22 patient records had significant missing data – both

these subsets were excluded. Two hundred thirty patients were included in the final analysis. Patient characteristics and treatment details are shown in table 1. Briefly, median age of the patient population was 53 (IQR, 42-60) years and 72% were male. Eighty-five percent had non-cardia gastric cancer. Most (76%) patients underwent D2 lymphadenectomy, and a median of 14 (range 0–53) lymph nodes were resected. Eighty-eight percent received adjuvant chemoradiotherapy while 12% received chemotherapy alone. 92% patients received 5-fluorouracil based chemotherapy; concurrent chemotherapy protocols between 2002 and 2013 used 5-fluorouracil + leucovorin (INT-0116 protocol), which was substituted by capecitabine from 2014 onwards. Most of those who underwent chemotherapy alone received capecitabine/oxaliplatin or FOLFOX regimen. Adverse events associated with AT are enumerated in Table 2. Diarrhea, neutropenia, and nausea/vomiting were the most common grade 3/4 toxicities; there were no treatment-related deaths. Approximately 86% of patients could complete full planned chemotherapy.

Adjuvant treatment was initiated at a median 42 (range 13 – 203) days after surgery; 17% started within 4 weeks, 55% between 4–8 weeks, and 28% after 8 weeks (Fig. 1). Median interval between gastrectomy and adjuvant treatment was 38 (range 13 – 56) days in the early AT group and 77 (range 57 – 203) days in the late AT group. The reasons for delay included poor general condition after gastrectomy, long waiting list for radiotherapy, post-operative complications (including anastomotic leak and surgical site infections), and patient preference. Baseline characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, stage, extent of surgery and lymph node dissection were similar between the early and late AT groups, except for a slightly higher proportion (91%) of non-cardia gastric cancer in the late AT group (versus 83% in the early AT group).

At the time of analysis, 100 patients had disease recurrence and 57 patients had died. The first site of recurrence was locoregional in six patients and distant in 7 patients, while 41 patients had both locoregional relapse and distant metastases. With a median follow-up of 28 months, 5-year RFS and OS for the full cohort were 42.3 ± 4.2% and 63.2 ± 4.4%, respectively (Fig. 2). Five-year RFS rates in the early and late AT groups were 45.5 ± 5.0% and 34.3 ± 7.6% (p = 0.005), respectively (Fig. 3a), and corresponding 5-year OS rates were 65.6 ± 5.3% and 52.9 ± 8.7% (p = 0.010) (Fig. 3b). On multivariate analysis, initiation of adjuvant therapy beyond 8 weeks was associated with a significantly higher risk for disease recurrence (hazard ratio (HR) 2.28; 95% CI, 1.29 – 4.04; p = 0.005) and death (HR 2.65; 95% CI, 1.27 – 5.52; p = 0.01). Other factors that independently predicted for a worse RFS were poor performance status and advanced disease stage; discontinuation of treatment was associated with higher risk for disease recurrence or death but missed statistical significance (Table 3). Poor performance status was also significantly associated with a higher risk for death, while disease stage was of borderline significance (Table 3). The extent of lymph node dissection, number of lymph nodes resected, microscopic margin positivity, and chemotherapy dose reduction for toxicity did not significantly affect the RFS or OS.

Discussion

The purpose of adjuvant treatment in any cancer is to eradicate clinically inapparent micrometastatic disease, leading to a higher probability for cure. Theoretically speaking, after radical surgery, there may be a small residual malignant clone, which is relatively easier to eradicate with early chemo(radio)therapy. Based on a mathematical model, Harless et al have shown that the chance for eradicating cancer is inversely proportional to the tumor bulk, which, among other factors, depends on the time elapsed between surgical resection and effective chemotherapy. The authors have likened cancer to a medical emergency and argued that a delay in adjuvant therapy may allow the residual malignant cell clone to proliferate and eventually become insurmountable (16). In patients with breast cancer, there is high-quality evidence that late initiation of AT results in inferior disease-free survival and overall survival, especially in the triple-negative breast cancer subset (13,17). Similarly, for stage III colorectal cancer, it has been established that adjuvant chemotherapy loses its efficacy with each passing week after surgery, and it may be futile if delayed beyond 21 weeks (11). However, there is lack of similar large studies in the case of stomach cancer.

Our report adds to the scant evidence that for patients with gastric cancer also, there may be reduced benefit from adjuvant treatment if it is delayed beyond 8 weeks after gastrectomy. The findings are in agreement with results of other studies from Korea and Taiwan (14,18). Park and colleagues were among the first to report that there is marked loss of efficacy of AT if the interval from gastrectomy exceeds 8 weeks (14). In their study, patients who started AT more than 8 weeks after surgery had significantly worse RFS and OS in comparison to patients who started it within 8 weeks. Two other series from Korea have suggested that AT must be started within 4 weeks of gastrectomy since OS is worse if the time to adjuvant chemotherapy exceeds 4 weeks (19,20). However, few points must be kept in mind when considering 4 weeks as the benchmark. Firstly, the patients in these studies did not receive adjuvant radiation, which is generally included for most patients who have not received any pre-operative treatment. Secondly, in the delayed AT group of the Kang et al study, there were significantly more patients who had developed post-operative complications – the inferior survival may be a reflection of post-operative morbidity or frailty (19). Lastly, in routine clinical practice, only a minority of patients have adequately recovered from gastrectomy to enable such early start of AT, thereby limiting the generalizability of these recommendations.

In contrast to patients undergoing surgery for other malignancies (e.g., breast) most patients with gastrointestinal cancer will require several weeks to recover and resume normal nutrition before they can receive adjuvant treatment. In the current series, though there was a small subset who managed to start AT within 2-3 weeks, majority of patients took approximately 4-6 weeks to recover sufficiently. Together with the report by Park et al, which suggested that there is no definite advantage to starting AT sooner than 4 weeks, our results indicate that the optimal timing to start adjuvant treatment may lie between 4 to 8 weeks after surgery (14). This recommendation for optimal timing of AT is also supported by a recently published meta-analysis (21).

Though conventional teaching may suggest that a delay in AT is likely to be detrimental, few reports did not find a survival benefit from early initiation of AT (15,22). A closer look at the report by Fujitani *et al*

reveals that most patients started chemotherapy within 6 weeks and their improved survival (HR 0.843; 95% CI, 0.60 – 1.18; p = 0.32) may have missed statistical significance (22). Similarly, Greenleaf and colleagues reported that in Western patients, there is no diminution of benefit from AT, even when it is delayed. This finding is in contrast to almost all the reports from East and may be due to differences in the patient population, extent of lymph nodal dissection (significant number of patients with <15 lymph nodes resected) or disease biology. Strangely, post-hoc analysis of a trial conducted in Italy found a positive association between treatment delay (>8 weeks) and disease-free survival (HR 0.95; 95% CI, 0.89 – 1.00) as well as overall survival (HR 0.91; 95% CI, 0.86 – 0.97) (23). This association, albeit weak, is rather counter-intuitive and the authors speculated that it may be due to better patient recovery translating into higher subsequent treatment compliance.

There are important implications of our findings. Our results provide clinicians with an optimal range within which AT should preferably be initiated after gastrectomy. After radical gastrectomy, it may be reasonable to allow approximately 4 weeks for convalescence, nutritional build-up and psychological preparation, but in the absence of peri-operative complications, AT should not be delayed beyond 8 weeks in order to retain its efficacy. Besides patient-related factors, there may be logistical reasons to delaying chemotherapy in the face of limited resources, which compel some oncology centres to create waiting lists for administration of chemotherapy and radiotherapy. In this setting, the current report will guide treating teams to appropriately prioritize gastric cancer patients. Our findings may also make a case for the use of minimal access surgical approaches over open resection, to hasten post-operative recovery and allow earlier institution of AT. However, this requires validation in a prospective study before it can be recommended.

Limitations

Our study has a few limitations – the most important being its largely retrospective patient population. However, considering that delaying AT beyond a time period that is reasonable for post-operative recovery can only be deleterious, it is unlikely that a randomized trial to assess the impact of delaying AT will ever be conducted for ethical reasons. Hence, the question of optimal timing can only be answered using large retrospective studies or meta-analyses. Secondly, since patient debility was the most common reason for deferring AT, we cannot definitively conclude if it was the delay itself or the patient's poor general condition that led to poor outcomes in this subset, since a poor performance status at diagnosis was independently associated with inferior RFS and OS. This interaction could have been explored if patient's performance status after surgery was available – but this metric was not recorded in most cases. Another limitation is the relatively short median follow-up; this is likely due to a significant number of patients being included from the latter half of the study duration. Lastly, subgroup analyses in prior reports have suggested that disease recurrence and survival may differ by the choice of chemotherapy, disease stage, and duration of chemotherapy (14,22). However, we did not perform a similar subgroup analysis due to a relatively small sample size, since it may lead to erroneous inferences.

Conclusion

In summary, our study results suggest that delaying AT beyond 8 weeks after radical gastrectomy is potentially detrimental to disease recurrence and survival in patients with stomach cancer. If patients have adequately recovered, AT should preferably be initiated within 8 weeks of surgery.

Abbreviations

AT – Adjuvant treatment

ECOG – Eastern Cooperative Oncology Group

IQR – Interquartile range

OS – Overall survival

RFS – Recurrence-free survival

Declarations

Ethics approval and consent to participate: The study protocol was approved by the institute ethics committee of All India Institute of Medical Sciences, New Delhi (Reference no. IECPG-424/27.06.2019). All patients enrolled prospectively provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication: Not applicable

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Authors' contributions:

SA: Conceptualization, methodology, data curation, formal analysis, writing–original draft, writing–review and editing. AS: Conceptualization, methodology, data curation, formal analysis, writing–original draft, writing–review and editing. BKM: Data acquisition, writing–review and editing. SP: Data acquisition, writing–review and editing, meaningful contributions. RP: Methodology, data acquisition, formal analysis, writing–review and editing. SVSD: Data acquisition, writing–review and editing. SK: Data acquisition, writing–review and editing. SP: Data acquisition, writing–review and editing. NRD: Data acquisition, writing–review and editing. NKS: Data acquisition, writing–review and editing. ST: Data acquisition,

writing–review and editing. VR: Data acquisition, writing–review and editing. All authors read and approved the final manuscript.

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Tables

Table 1. Patient characteristics

Parameter	Mean (± SD) or Median (IQR)		
	All patients	Early group	Delayed group
	N = 230	N = 165	N = 65
Age at diagnosis, years	51.2 (± 12.7)	50.3 (± 13.2)	53.6 (± 11.6)
Sex			
Male	165 (72%)	121 (73%)	44 (68%)
Female	65 (28%)	44 (27%)	21 (32%)
ECOG PS (n = 142)			
0	14 (10%)	13 (14%)	1 (2%)
1	105 (74%)	66 (70%)	39 (81%)
2	23 (16%)	15 (16%)	8 (17%)
Gastrectomy (n = 229)			
Subtotal	161 (70%)	114 (70%)	47 (72%)
Total	68 (30%)	50 (30%)	18 (28%)
Lymph node dissection (n = 228)			
D1	58 (24%)	47 (28%)	11 (17%)
D2	170 (76%)	118 (72%)	52 (83%)
Tumor location (n = 229)			
Pylorus	113 (49%)	78 (48%)	35 (54%)
Body	53 (23%)	39 (24%)	14 (22%)
Gastroesophageal junction	34 (15%)	28 (17%)	6 (9%)
Body and pylorus	22 (10%)	15 (9%)	7 (11%)
Fundus and body (label 5)	4 (2%)	2 (1%)	2 (3%)
Fundus	1 (< 1%)	1 (0.6%)	0
Not specified	2 (< 1%)	1 (0.6%)	1 (2%)
Lauren classification histology (n = 32)			
Intestinal	22 (69%)	14 (64%)	8 (80%)
Diffuse	10 (31%)	8 (36%)	2 (20%)
Degree of differentiation (n = 113)			
Well differentiated	10 (9%)	5 (7%)	5 (13%)

Moderately differentiated	47 (42%)	29 (39%)	18 (46%)
Poorly differentiated	56 (49%)	40 (54%)	16 (41%)
Signet ring cell morphology (n = 226)			
Present	79 (35%)	55 (34%)	24 (38%)
Absent	147 (65%)	107 (66%)	40 (62%)
Her2neu immunohistochemistry (n = 22)			
Positive	14 (64%)	11 (58%)	3 (100%)
Negative	7 (32%)	7 (37%)	0
Equivocal	1 (4%)	1 (5%)	0
Lymph nodes resected (n = 225)			
Median (IQR)	14 (7-20)	13 (7-19)	16 (10-22)
16 or more	99 (44%)	67 (41%)	32 (51%)
Less than 16	126 (56%)	95 (59%)	31 (49%)
Margin status (n = 223)			
R0	191 (86%)	138 (86%)	53 (85%)
R1	32 (14%)	23 (14%)	9 (15%)
AJCC 7th edition stage group (n = 228)			
I	8 (3%)	3 (2%)	5 (8%)
II	63 (27%)	46 (28%)	17 (27%)
III	157 (69%)	115 (70%)	42 (66%)
Time to adjuvant treatment			
Median (IQR), days	42 (33-61)	38 (30-45)	77 (66-91)
Adjuvant treatment			
Chemotherapy only	27 (12%)	17 (16%)	10 (15%)
Chemoradiotherapy	203 (88%)	89 (84%)	55 (85%)
Chemotherapy			
Capecitabine	63 (27%)	38 (23%)	25 (39%)
5-fluorouracil + leucovorin	127 (55%)	101 (61%)	26 (40%)
Capecitabine + Oxaliplatin	23 (10%)	15 (9%)	8 (12%)
Paclitaxel + Carboplatin	12 (5%)	8 (4%)	4 (6%)

FOLFOX	1 (<1%)	1 (<1%)	0
Other	4 (2%)	2 (1%)	2 (3%)

SD = standard deviation, IQR = interquartile range, ECOG PS = Eastern Cooperative Oncology Group performance status, AJCC = American Joint Committee on Cancer

Table 2. Treatment toxicity and completion

Toxicity	Incidence (Percentage)	
	Any grade	Grade 3-4
Neutropenia	76 (33%)	30 (13%)
Febrile neutropenia	11 (5%)	11 (5%)
Anemia	132 (57%)	6 (3%)
Thrombocytopenia	79 (34%)	13 (6%)
Nausea/vomiting	53 (23%)	25 (11%)
Mucositis	36 (16%)	18 (8%)
Hand foot syndrome	9 (4%)	3 (1%)
Fatigue	10 (4%)	1 (0.4%)
Diarrhea	75 (33%)	52 (23%)
Neuropathy	13 (6%)	1 (0.4%)
Hypoalbuminemia	67 (29%)	2 (0.8%)
Metabolic	28 (12%)	3 (1.3%)
Hepatic	2 (0.9%)	-
Renal	3 (1.3%)	1 (0.4%)
Cardiac	-	-
Toxic death	-	-
Parameter		**Number of patients (%)**
Chemotherapy completion (n = 220)		
Received all planned cycles		189 (86%)
Discontinued treatment		31 (14%)
Chemotherapy dose reduction (n = 211)		
Received planned doses		163 (77%)
Required dose reduction		48 (23%)
Radiotherapy completion (n = 193)		
Received all planned radiation		184 (95%)
Discontinued treatment		9 (5%)

Table 3. Prognostic factors for disease recurrence and death

Predictor	n	5-year RFS	HR (95% CI)	P-value[a]	5-year OS	HR (95% CI)	P-value[a]
ECOG performance status							
0 or 1	119	49.6 ± 5.2%	1		68.9 ± 5.1%	1	
2	23	30.7 ± 10.1%	1.99 (0.99 – 3.99)	**0.050**	42.8 ± 12.7%	2.56 (1.11 – 5.91)	**0.027**
Lymph node dissection							
D1 dissection	57	23.4 ± 8.8%	1		41.5 ± 11.8%	1	
D2 dissection	167	46.2 ± 4.7%	0.91 (0.36 – 2.30)	0.846	67.7 ± 4.7%	0.79 (0.25 – 2.48)	0.685
Number of lymph nodes resected							
Less than 16	123	37.8 ± 6.0%	1		66.3 ± 6.2%	1	
At least 16	99	44.0 ± 5.9%	1.02 (0.68 – 1.51)	0.976	57.5 ± 6.5%	1.24 (0.73 – 2.11)	0.459
Resection margin status							
R0 resection	188	48.1 ± 4.7%	1		66.7 ± 4.8%	1	
R1 resection	32	16.6 ± 7.4%	1.45 (0.64 – 3.28)	0.366	46.3 ± 10.2%	1.45 (0.52 – 4.04)	0.481
AJCC Stage group							
I	8	80.0 ± 17.9%	1		80.0 ± 17.9%	1	
II	61	56.3 ± 7.9%	1.74 (0.41 – 7.41)		74.8 ± 7.6%	0.89 (0.20 – 4.02)	
III	155	32.6 ± 4.9%	3.44 (0.84 – 14.05)	**0.007**	54.4 ± 5.8%	2.06 (0.50 – 8.57)	0.058
Time to adjuvant treatment							
Up to 8 weeks	161	45.5 ± 5.0%	1		65.6 ± 5.3%	1	
	65	34.3 ± 7.6%		**0.005**	52.9 ± 8.7%		**0.010**

More than 8 weeks			2.28 (1.29 – 4.04)			2.65 (1.27 – 5.52)	
Chemotherapy completion							
Received all planned cycles	185	45.3 ± 4.7%	1		65.6 ± 4.8%	1	
Discontinued treatment	31	29.4 ± 10.4%	1.97 (0.97 – 4.01)	0.060	50.9 ± 12.3%	1.97 (0.77 – 5.03)	0.154
Chemotherapy dose reduction							
Received planned doses	159	46.4 ± 5.1%	1		65.6 ± 5.2%	1	
Required dose reduction	48	27.3 ± 8.5%	1.61 (0.88 – 2.94)	0.125	50.1 ± 11.2%	1.41 (0.65 – 3.05)	0.383

a = multivariate log-rank *p*-value; RFS = Recurrence free survival; OS = Overall survival; HR = Hazard ratio; CI = Confidence intervals; ECOG = Eastern cooperative oncology group; AJCC = American Joint Committee on Cancer

Figures

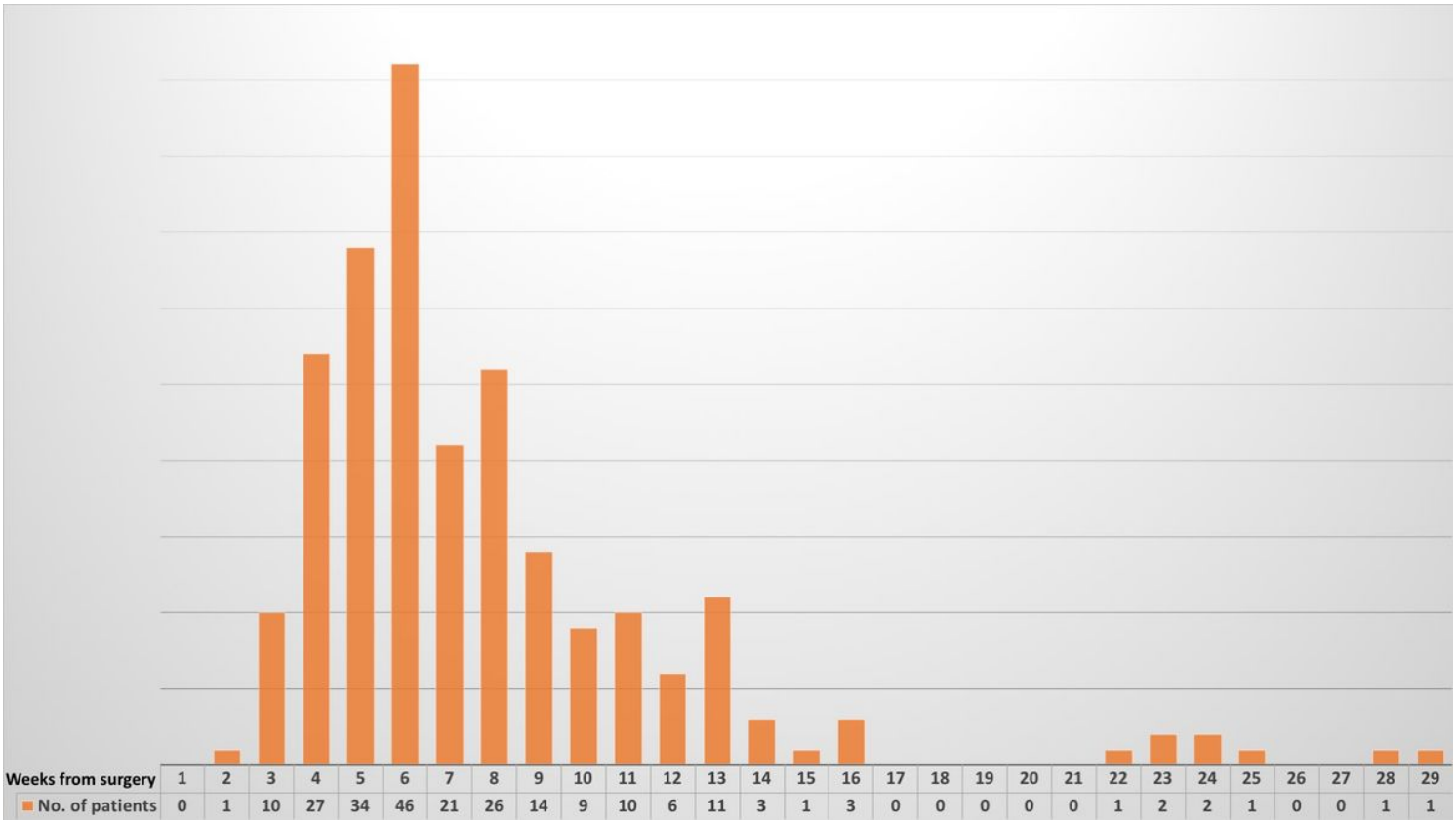

Figure 1

Time interval between radical gastrectomy and adjuvant therapy

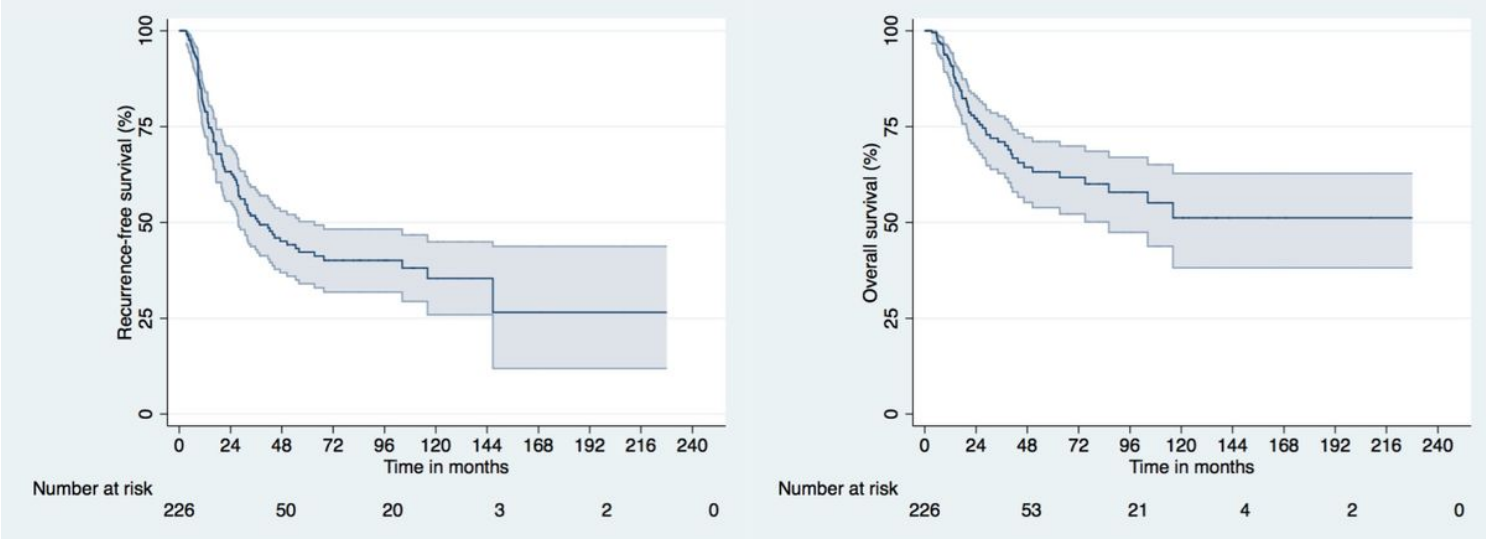

Figure 2

(a) Recurrence free survival for all patients with 95% confidence intervals, and (b) Overall survival for the full cohort with 95% confidence intervals

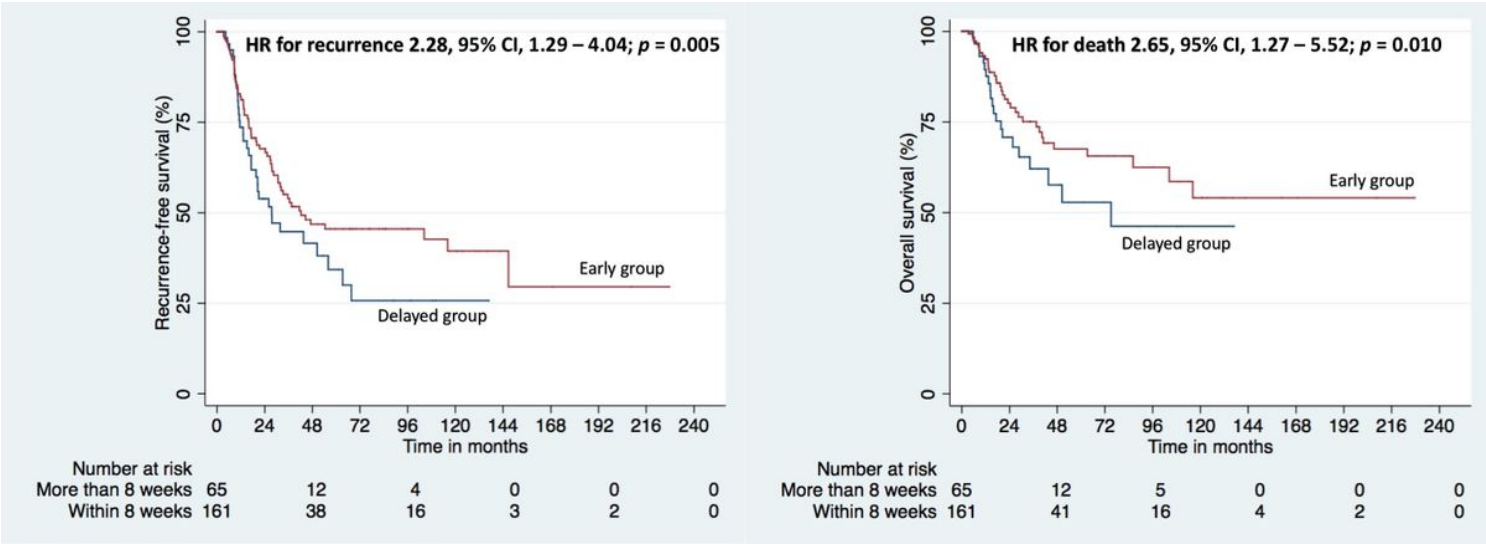

Figure 3

(a) Recurrence free survival by time to adjuvant treatment, and (b) Overall survival by time to adjuvant treatment