

Impact of delay in adjuvant chemotherapy on survival in resected gastric cancer: Real world data from India



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Background

- Surgical resection is the primary curative modality for invasive gastric cancer, but most patients require adjuvant chemoradiation to prevent locoregional or distant relapse.
- 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.
- In routine clinical management of gastrointestinal cancers, AT is frequently delayed due to inadequate recovery from surgery, general patient debility, and surgical complications (e.g., wound infections and anastomotic leaks).

Objectives

- To assess 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: Single center ambispective cohort study
- Study population and period: All patients who underwent upfront curative intent surgical resection followed by adjuvant chemoradiation or chemotherapy for stages I-III gastric cancer at All India Institute of Medical Sciences, New Delhi, from January 2002 through December 2019
- Patients who received neoadjuvant chemotherapy or had non-adenocarcinoma histology were excluded
- Predictors of recurrence-free survival (RFS) and overall survival (OS) were determined using Cox proportional hazards model

Results

- Two hundred thirty patients were included in the analysis; baseline characteristics are listed in Table 1
- Eighty five percent patients had non-cardia gastric cancer
- 88% patients received adjuvant chemoradiation while 12% received chemotherapy alone
- 5-fluorouracil and leucovorin (INT-0116 protocol) were used as the chemotherapeutic agent until 2013, which was replaced by capecitabine 2014 onwards
- Patients were categorized into two groups based in interval between gastrectomy and AT initiation – early group (within 8 weeks) and delayed group (after 8 weeks).
- Reasons for delay: poor general condition after gastrectomy, long waiting list for radiotherapy, post-operative complications (including anastomotic leak and surgical site infections), and patient preference
- 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

Figure 1) RFS and OS for all patients

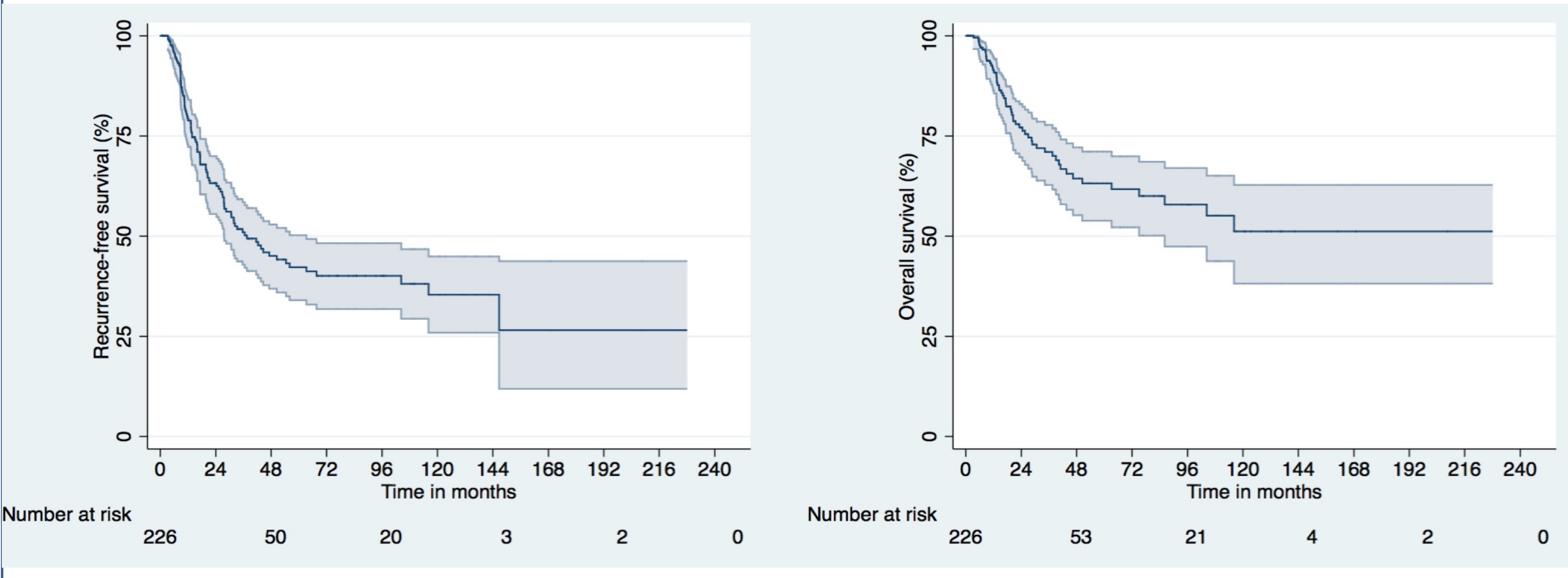


Table 1) Baseline characteristics

Parameter	Mean (± SD) or Median (IQR)		
	All patients N = 230	Early group N = 165	Delayed group 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%)
Lymph node dissection (n = 228)			
D1	58 (24%)	47 (28%)	11 (17%)
D2	170 (76%)	118 (72%)	52 (83%)
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 7 th 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)

Figure 2) Time to initiation of adjuvant treatment after radical gastrectomy

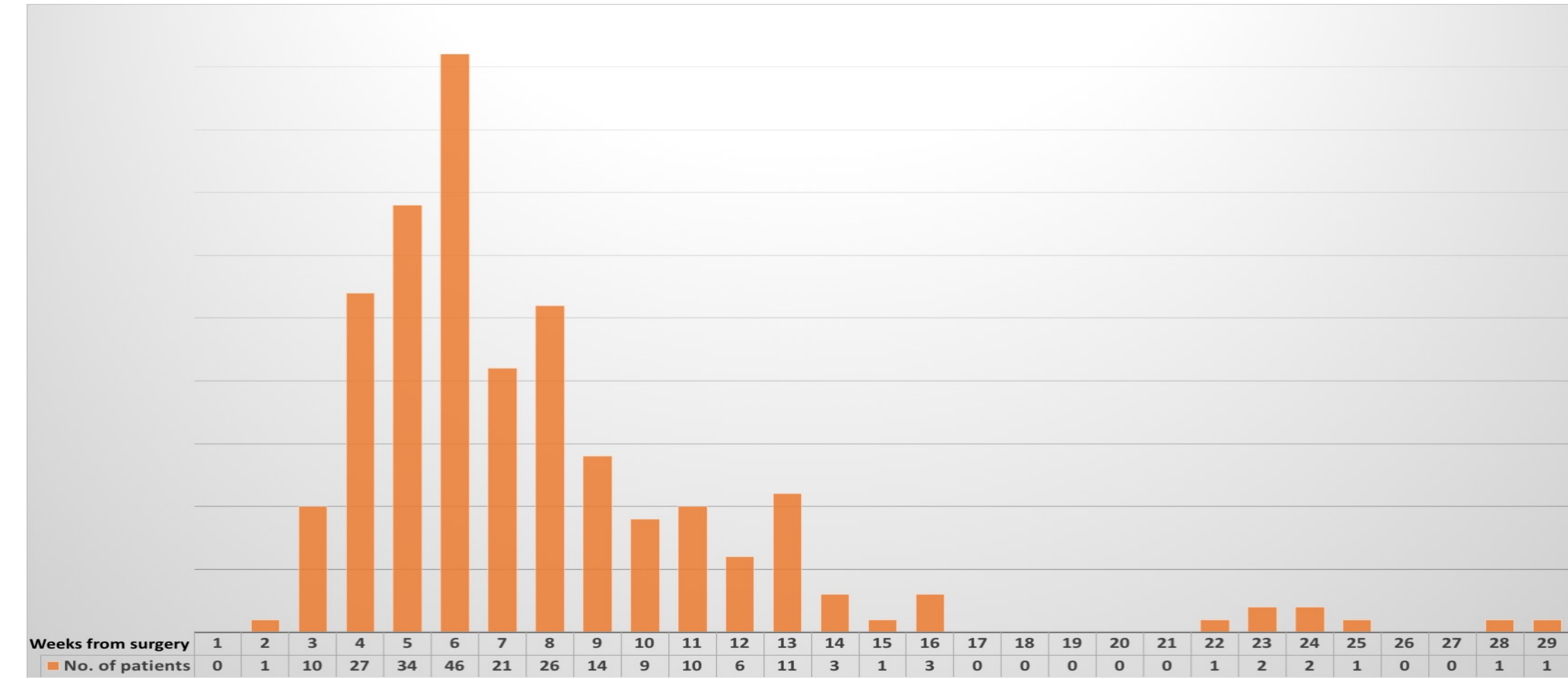
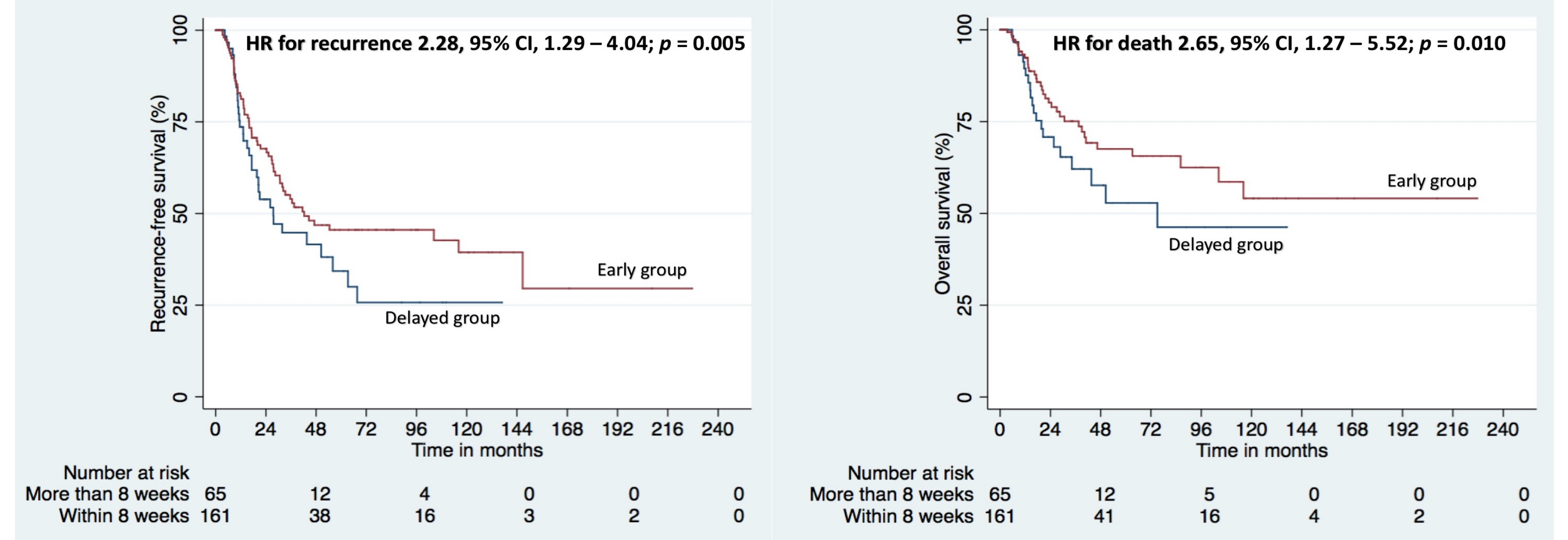


Table 2) Predictors of recurrence-free survival and overall survival

Predictor	n	5-year RFS	HR (95% CI)	P-value	5-year OS	HR (95% CI)	P-value
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 7 th ed 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	
More than 8 weeks	65	34.3 ± 7.6%	2.28 (1.29 – 4.04)	0.005	52.9 ± 8.7%	2.65 (1.27 – 5.52)	0.010

Figure 3) Recurrence-free survival and overall survival by time to adjuvant treatment



Conclusions

- Adjuvant treatment in stomach cancer is aimed at eradication of clinically inapparent micrometastatic disease, leading to a higher probability for cure. After radical surgery, there may be a small residual malignant clone, which is relatively easier to eradicate with early chemoradiotherapy.
- If adjuvant chemoradiotherapy is delayed beyond 8 weeks after radical gastrectomy, there is significant loss of its efficacy, with a resultant higher risk of disease recurrence and death
- If patients have adequately recovered from surgery and in the absence of perioperative complications, adjuvant therapy should be initiated within 8 weeks of surgery

Limitations

- Retrospective nature of study; however, the impact of delay cannot be assessed prospectively due to ethical concerns
- Relatively small sample size and single institutional data

Financial disclosures / Conflict of interest

- All authors declare no conflict of interest

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