

Timing of chemotherapy and survival in patients with resectable gastric adenocarcinoma

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Abstract

AIM: To evaluate the timing of chemotherapy in gastric cancer by comparing survival outcomes in treatment groups.

METHODS: Patients with surgically resected gastric adenocarcinoma from 1988 to 2006 were identified from the Los Angeles County Cancer Surveillance Program. To evaluate the population most likely to receive and/or benefit from adjunct chemotherapy, inclusion criteria consisted of Stage II or III gastric cancer patients > 18 years of age who underwent curative-intent

surgical resection. Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) preoperative chemotherapy; or (3) postoperative chemotherapy. Clinical and pathologic characteristics were compared across the different treatment arms.

RESULTS: Of 1518 patients with surgically resected gastric cancer, 327 (21.5%) received perioperative chemotherapy. The majority of these 327 patients were male (68%) with a mean age of 61.5 years; and they were significantly younger than non-chemotherapy patients (mean age, 70.7; $P < 0.001$). Most patients had tumors frequently located in the distal stomach (34.5%). Preoperative chemotherapy was administered to 11.3% of patients ($n = 37$) and postoperative therapy to 88.7% of patients ($n = 290$). An overall survival benefit according to timing of chemotherapy was not observed on univariate or multivariate analysis. Similar results were observed with stage-specific survival analyses (5-year overall survival: Stage II, 25% vs 30%, respectively; Stage III, 14% vs 11%, respectively). Therefore, our results do not identify a survival advantage for specific timing of chemotherapy in locally advanced gastric cancer.

CONCLUSION: This study supports the implementation of a randomized trial comparing the timing of perioperative therapy in patients with locally advanced gastric cancer.

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Key words: Chemotherapy; Gastric cancer; Adjunct therapy; Postoperative therapy; Preoperative therapy; Timing

Core tip: Curative intent surgical resection offers the

best survival potential in conjunction with chemotherapy for patients with gastric cancer. Few studies have evaluated the optimal timing of chemotherapy. This study shows that in the setting of resectable gastric cancer, there is no survival advantage based on the timing of chemotherapy.

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INTRODUCTION

Despite an overall decrease in the incidence and mortality in gastric cancer patients in the United States, nearly 22000 patients will be diagnosed with gastric cancer in the United States each year^[1]. More alarmingly, gastric cancer remains the 2nd leading cause of cancer-related deaths worldwide accounting for an estimated 436930 deaths in 2013^[2,3]. In Western societies, where screening is not routine (compared to Asian countries^[4,5]), the majority of patients present with regional or distant disease^[6,7], and the 5-year overall survival is 30%-40%^[8-10]. In these cases, the only hope for long term survival remains surgical resection with curative intent^[11]. Despite aggressive surgical measures, rates of disease recurrence remain high following surgery^[12,13]. In fact, approximately 50% to 90% of patients die as a result of disease relapse^[14]. As a result, much attention has been placed on the identification of optimal adjunct therapies for gastric cancer.

Adjunct therapies for gastric cancer may be administered in the pre-operative (*i.e.*, neoadjuvant) or post-operative (*i.e.*, adjuvant) settings. Multiple trials have assessed these treatment strategies; and potential benefits have been drawn from both options^[14-19]. In a landmark study, the investigators of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial reported an overall survival benefit with a regimen that incorporated neoadjuvant and adjuvant (*i.e.*, peri-operative) timing of chemotherapy consisting of epirubicin, cisplatin, and fluorouracil (ECF) when compared to surgery alone^[18]. From the Intergroup 0116 trial, investigators reported a 9 mo improvement in survival (27 mo *vs* 36 mo) when adjuvant chemoradiation was administered compared to surgery alone^[17]. More recently, the CLASSIC trial investigators reported an overall survival benefit from adjuvant chemotherapy (capecitabine and oxaliplatin) compared to surgery alone^[20]. However, there has been no trial that has directly compared neoadjuvant versus adjuvant chemotherapy administration. Using a large, population-based cohort, the objective of this study was to assess whether the timing of chemotherapy affects the survival of patients following surgical

resection for gastric cancer.

MATERIALS AND METHODS

Los Angeles County Cancer Surveillance Program

The Los Angeles County (LAC) Cancer Surveillance Program (CSP) is the cancer registry that collects information for all cancer diagnoses in LAC since 1972. As part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program, CSP routinely collects data on patient demographics, primary tumor site, tumor morphology, disease stage at diagnosis, treatment received, and follow-up. CSP monitors the quality of data by performing annual reviews and training of staff. Approval to conduct this study was obtained from the Institutional Review Boards of the City of Hope and the State of California.

CSP tumor coding and study criteria

Using the CSP registry, we identified patients diagnosed with gastric adenocarcinoma from 1988 to 2006. Inclusion criteria consisted of Stage II or III gastric cancer patients above 18 years of age who underwent curative-intent surgical resection. As Stage I disease is more likely to be treated by surgery alone and patients with Stage IV disease are more likely not to undergo surgery given metastatic/unresectable disease, these patients were excluded from the current study. Therefore, this study was designed to evaluate the population most likely to receive and/or benefit from adjunct chemotherapy (Stage II or III).

Specifically, we included only gastric cancer patients with International Classification of Diseases for Oncology histology codes for adenocarcinoma: 8140-8145, 8210-8211, 8480-8481, and 8490. In CSP, the location of tumor was categorized as proximal, distal, middle, or whole stomach. For each patient, stage was categorized according to the American Joint Commission on Cancer (AJCC) 7th Edition classification system. Furthermore, size and depth of tumor invasion were categorized by AJCC T-stage as: T1A, T1B, T2, T3, or T4. The presence or absence of nodal involvement was designated by AJCC N-stage as: N0, N1, N2, or N3. Our survival analysis included only patients with AJCC Stage II and III gastric cancer. Finally, we obtained data regarding the timing of chemotherapy administration (none, preoperative, or postoperative). As the CSP database only codes the date of the first chemotherapy treatment, patients who did receive preoperative (neoadjuvant) chemotherapy may or may not have received subsequent postoperative chemotherapy. Therefore, we could not distinguish between neoadjuvant and perioperative chemotherapy in this database. Thus, this study compares neoadjuvant chemotherapy, adjuvant chemotherapy, and no chemotherapy.

Statistical analysis

Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) neoadjuvant chemotherapy (\pm postoperative chemother-

Table 1 Comparison of the characteristics of the surgical groups *n* (%)

Characteristic		No chemo <i>n</i> = 1191	Received chemotherapy <i>n</i> = 327	<i>P</i> value
Age, yr	Mean ± SD	71 ± 12	61 ± 14	< 0.0001
Sex	Men	741 (62)	221 (68)	0.0743
	Women	450 (38)	106 (32)	
Race/ ethnicity	Non-hispanic white	438 (37)	118 (36)	0.9833
	Black	112 (9)	33 (10)	
	Hispanic white	322 (27)	88 (27)	
	Asian/pacific islanders	319 (27)	88 (27)	
Tumor location	Proximal	296 (25)	98 (30)	0.0290
	Distal	423 (36)	100 (31)	
	Whole	167 (14)	59 (18)	
	Middle	305 (26)	70 (21)	
Grade	Well differentiated	26 (2)	1 (0)	0.0178
	Moderately differentiated	312 (26)	70 (21)	
	Poorly differentiated	792 (66)	234 (72)	
	Undifferentiated	40 (3)	18 (6)	
	Unknown	21 (2)	4 (1)	
Tumor size	≤ 5 cm	462 (39)	117 (36)	0.6048
	>5 cm	507 (43)	145 (44)	
	Unknown	222 (19)	65 (20)	
T stage ¹	T2	108 (9)	24 (7)	0.1556
	T3	620 (52)	163 (50)	
	T4a	319 (27)	96 (29)	
	T4b	144 (12)	44 (13)	
	T4c	334 (28)	38 (12)	
N stage ¹	N0	334 (28)	38 (12)	< 0.0001
	N1	786 (66)	261 (80)	
	N2	31 (3)	15 (5)	
	N3	40 (3)	13 (4)	
Node status	N-	334 (28)	38 (12)	< 0.0001
	N+	857 (72)	289 (88)	
AJCC7 group	II	767 (64)	187 (57)	0.0168
	III	424 (36)	140 (43)	

¹*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

apy); or (3) adjuvant chemotherapy.

Clinical and pathologic characteristics were compared across the different treatment arms by χ^2 analyses for categorical variables and student's *t* test for continuous variables. Cox-proportional hazards modeling was used to evaluate the role of chemotherapy and other variables on overall survival as represented by hazard ratios (HR) with 95%CI. Variables included in the univariate analyses were age, sex, race/ethnicity, tumor location, AJCC stage, T-stage, N-stage, tumor grade, tumor size, lymph node number, and timing of chemotherapy regimen (neoadjuvant ± adjuvant *vs* adjuvant alone). Variables included in the multivariate analyses were age, AJCC stage, and timing of chemotherapy regimen (preoperative *vs* postoperative). Because tumor size, T stage and lymph node status are multi-collinear with AJCC stage, the multivariate model included AJCC stage alone to represent the staging variable.

Survival was defined as survival throughout the study period (1988-2006). Mortality was defined through the database used as all-cause mortality since date of diagnosis of gastric cancer. Overall survival (OS) for the treat-

ment arms was calculated by the Kaplan-Meier method, and differences in survival were compared by the log-rank test. Proportional hazard assumptions for the Cox models were tested by calculating scaled Schoenfeld residuals with results indicating model fit. Two-sided *P* values < 0.05 were considered to be statistically significant. All statistical analyses were completed using SAS software, (SAS institute Inc. Cary, NC).

RESULTS

Patient and tumor demographics

Of 1518 patients with AJCC Stage II or III surgically resected gastric cancer between 1988 and 2006, 22% of patients (*n* = 327) received chemotherapy as part of their cancer treatment. The demographics of the study cohort are presented in Table 1. Most tumors were observed in the proximal (26%) or distal stomach (35%) and were poorly differentiated (68%) by histology. The majority (76%) of the study cohort had lymph node positive disease; and most patients had Stage II disease (63%) rather than Stage III disease (37%). Patients who did not receive chemotherapy were more likely to have lymph node negative disease than those who did receive chemotherapy (28% *vs* 12%, *P* < 0.001).

Comparison of patients by treatment group

As shown in Table 1, patients who did not receive chemotherapy were older than those who did (71 *vs* 61, respectively, *P* < 0.001). Within the chemotherapy groups (Table 2), more patients received adjuvant chemotherapy (*n* = 290, 89%) than neoadjuvant chemotherapy (*n* = 37, 11%, *P* < 0.001). The mean ages of patients receiving chemotherapy were similar (65 and 61 years, neoadjuvant and adjuvant, respectively). The majority of patients were male in both chemotherapy groups. There was no difference in race/ethnicity, tumor location, tumor grade, T stage, N stage, node status or AJCC stage group.

Survival by treatment group and univariate and multivariate analysis

Patients who received chemotherapy were compared according to the timing of administration of chemotherapy (neoadjuvant *vs* adjuvant). By Kaplan-Meier method, a difference in overall survival was not observed between the neoadjuvant *vs* adjuvant chemotherapy groups (Figure 1A). This was consistent when the groups were evaluated by stage of disease as well (Figure 1B and C). Next, univariate and multivariate analyses were performed to identify factors associated with improved survival (Table 3). In univariate analysis, younger age, lower T stage, node negative status and Stage II disease were associated with improved survival. On multivariate analysis, older age and Stage III disease were independently associated with shorter survival. All other factors fell out of multivariate analysis and were not significant. When grouped by stage, age continued to be an independent predictor of survival in both the Stage II and III gastric cancer patients (data

Table 2 Comparison of characteristics by chemotherapy groups *n* (%)

Characteristic		Neoadjuvant <i>n</i> = 37	Adjuvant <i>n</i> = 290	<i>P</i> value
Age, yr	Mean (± SD)	65 (± 10)	61 (± 14)	0.0583
Sex	Men	23 (62)	198 (68)	0.4543
	Women	14 (38)	92 (32)	
Race/ ethnicity	Non-hispanic white	18 (49)	100 (34)	0.2885
	Black	3 (8)	30 (10)	
	Hispanic white	6 (16)	82 (28)	
	Asian/pacific islanders	10 (27)	78 (27)	
Tumor location	Proximal	12 (32)	86 (30)	0.9189
	Distal	10 (27)	90 (31)	
	Whole	6 (16)	53 (18)	
	Middle	9 (24)	61 (21)	
Grade	Well differentiated	0 (0)	1 (0)	0.9087
	Moderately differentiated	7 (19)	63 (22)	
	Poorly differentiated	27 (73)	207 (71)	
	Undifferentiated	2 (5)	16 (6)	
	Unknown	1 (3)	3 (1)	
Tumor size	≤ 5 cm	10 (27)	107 (37)	0.2297
	> 5 cm	16 (43)	129 (44)	
	Unknown	11 (30)	54 (19)	
T stage ¹	T2	0 (0)	24 (8)	0.4283
	T3	19 (51)	144 (50)	
	T4a	15 (41)	81 (28)	
	T4b	3 (8)	41 (14)	
N stage ¹	N0	7 (19)	31 (11)	0.2684
	N1	27 (73)	234 (81)	
	N2	1 (3)	14 (5)	
	N3	2 (5)	11 (4)	
	Node status	N-	7 (19)	
AJCC7 group	N+	30 (81)	259 (89)	0.5160
	II	23 (62)	164 (57)	
	III	14 (38)	126 (43)	

¹*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

not shown).

DISCUSSION

Despite advances in medical and surgical therapies, the prognosis of advanced gastric cancers remains poor, with a dismal 5-year relative survival rate of 28%^[1]. With locoregional and distant recurrence rates approaching > 70%, an emphasis has been placed on identifying effective adjunct therapeutic regimens^[18,17,20-23]. Systemic chemotherapy has been a logical choice, but the optimal timing of its administration remains unclear. In this study we compared the outcomes of Stage II-III surgically resected gastric cancer patients who received neoadjuvant (± postoperative chemotherapy) versus adjuvant chemotherapy and observed no difference in overall survival between the two treatment groups.

Several trials have examined the use of chemotherapy in the management of gastric cancer. One landmark study, the MAGIC trial by Cunningham *et al.*^[18], showed that perioperative chemotherapy with ECF decreased tumor size and stage while improving both progression-

free and overall survival when compared to surgery alone. In this randomized controlled prospective study, 503 patients were randomly assigned to either perioperative ECF chemotherapy (three cycles preoperative and three cycles postoperative) or surgery alone. Of the perioperative group, only 41.6% completed all six cycles of chemotherapy due to disease progression, toxic effects, or complications^[18]. The use of neoadjuvant chemotherapy decreased tumor size (3 cm *vs* 5 cm, *P* < 0.001) and stage of the pathologic surgical specimens. Therefore, by administering chemotherapy neoadjuvantly, the chance of curative resection by downstaging the tumor is increased. Other benefits of neoadjuvant chemotherapy include the elimination of micrometastasis, the improvement of tumor-related symptoms, and the determination of whether the tumor is chemotherapy-sensitive^[18]. The MAGIC trial concluded perioperative chemotherapy should be considered in patients with resectable gastric cancers. Although we observed no difference between neoadjuvant and adjuvant timing of chemotherapy, nevertheless our findings suggest that patients with Stage II or Stage III gastric cancer indeed benefit from chemotherapy in conjunction with surgery. The 3-year OS was 16.6% in the MAGIC trial compared to 35% and 37% in the neoadjuvant and adjuvant arms, respectively, in our study. Given the inherent limitations of our database, we could not assess the effect of neoadjuvant chemotherapy on downstaging the gastric cancer, an outcome also not reported in the MAGIC trial.

The use of adjuvant chemotherapy has also been a treatment choice in the setting of chemotherapy. Adjuvant chemotherapy provides the benefit of removing disease burden upfront with a surgical resection, followed by chemotherapy. The potential downfall of adjuvant chemotherapy is the delay in beginning systemic treatment in the postoperative period for recovery from surgery. Further, downstaging tumor is not possible with adjuvant chemotherapy. Bang *et al.*^[20] evaluated the use of adjuvant chemotherapy after gastrectomy with D2 lymph node dissection in patients with Stage II-III B gastric cancer in the recent CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) trial. In this phase III randomized controlled, multi-institutional study, 1035 patients were randomized to surgery alone or surgery followed by chemotherapy (capecitabine plus oxaliplatin). The CLASSIC trial found a 34% reduction in the risk of death in the chemotherapy arm (HR = 0.66, 95%CI: 0.51-0.85; *P* = 0.0015) and a 5-year overall survival that was significantly increased in the chemotherapy arm (78% chemotherapy arm *vs* 69% surgery alone arm, *P* < 0.0029)^[20,24]. However, the CLASSIC trial was reported in an eastern hemisphere patient population and has not been readily accepted in the United States^[20,24]. Further, the CLASSIC trial had a 56% rate of grade 3 or 4 adverse effects (neutropenia, nausea, and vomiting) requiring dose modifications in a significant portion of patients, thereby limiting completion of adjuvant therapy^[20].

The MAGIC and CLASSIC trials, however, did not

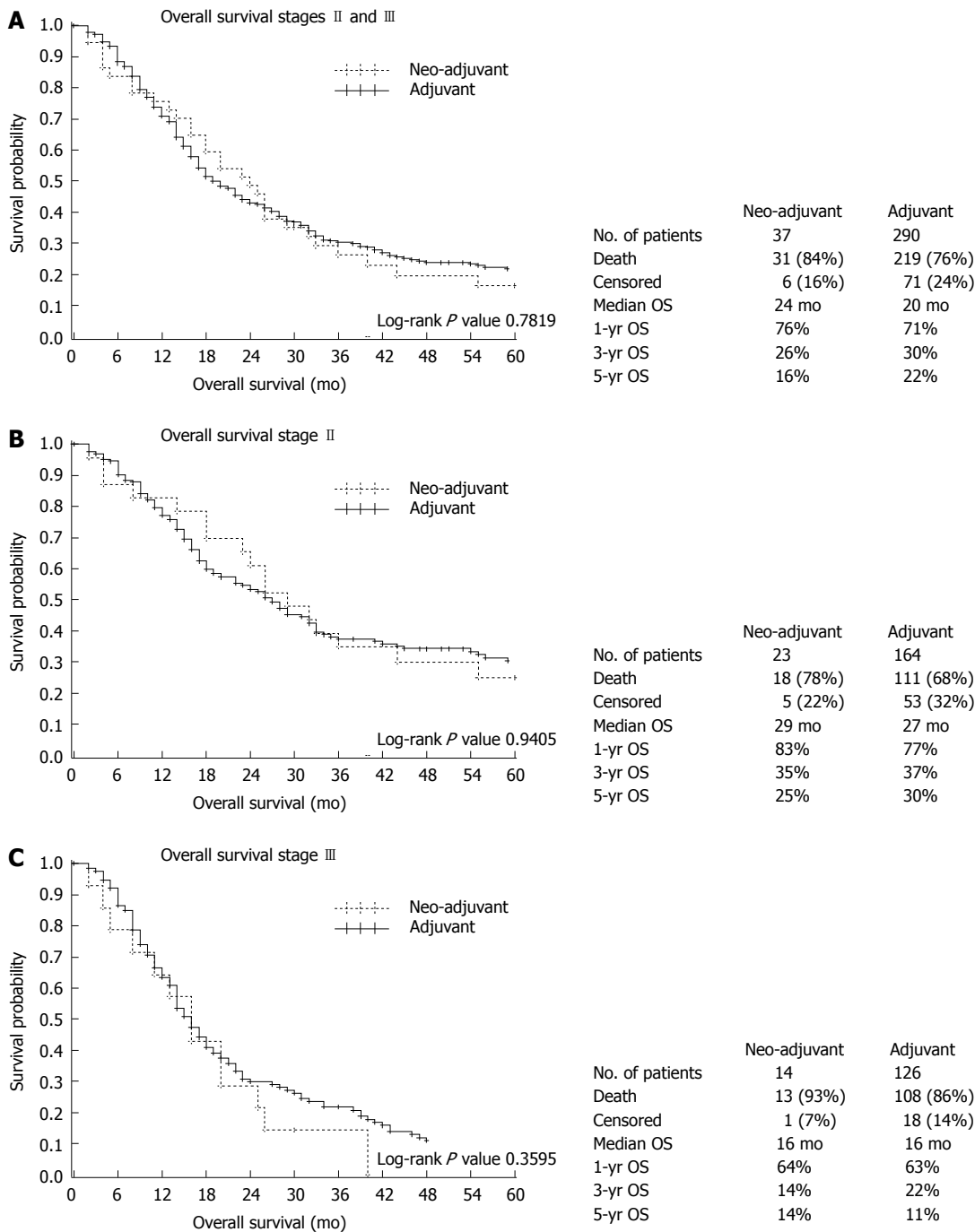


Figure 1 Comparison of Kaplan-Meier survival curves. A: For Stage II and III gastric cancer patients who underwent preoperative chemotherapy compared to those who had postoperative chemotherapy (MS 24 mo vs 20 mo, respectively; *P* = 0.7819); B: Stage II gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 29 mo vs 27 mo, respectively; 5-yr operating system (OS) 25% vs 30%; *P* = 0.9405); C: Stage III gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 16 mo vs 16 mo, respectively; 5-yr OS 14% vs 11%; *P* = 0.3595).

examine the role and timing of radiation for gastric cancer. Adjuvant chemoradiation has been shown to improve overall survival in patients with locally advanced gastric cancer. Macdonald *et al.*^[16,17,25-27] reported in the INT0116 Phase III randomized multi-institutional trial of adjuvant chemoradiation compared to surgery alone that adjuvant chemoradiation improved overall survival and disease-free survival. Though Macdonald *et al.*^[16,17,25-27] evaluated adjuvant chemoradiation to surgery alone, there are no

phase III trials that directly compare neoadjuvant with adjuvant chemoradiation. With the database used for this study, only receipt of radiation could be determined. Therefore, we could not assess the timing of radiation in relation to surgery and to exclude bias of radiation in our analysis, patients who received radiation were excluded from this current study.

Our study is not without its limitations. Due to the retrospective nature of this study, there may be patient

Table 3 Univariate and multivariate analysis

Factor	n (%)	Univariate		Multivariate	
		HR (95%CI)	P value	HR (95%CI)	P value
Chemo status ¹	Neo-Adjuvant	37 (11)	-	-	-
	Adjuvant	290 (89)	0.95 (0.65-1.38)	0.7854	0.97 (0.67-1.43) 0.8961
Age ¹ , yr	Mean ± SD	61.5 ± 14	1.02 (1.01-1.03)	0.0008	1.02 (1.01-1.03) 0.0006
Sex	Men	221 (68)	-	-	-
	Women	106 (32)	1.00 (0.77-1.31)	0.9859	-
Race/ethnicity	Non-hispanic white	118 (36)	-	-	-
	Black	33 (10)	1.48 (0.96-2.27)	0.0765	-
	Hispanic white	88 (27)	1.16 (0.84-1.59)	0.3576	-
	Asian/pacific islanders	88 (27)	1.00 (0.73-1.37)	1.0000	-
Tumor location	Proximal	98 (30)	-	-	-
	Distal	100 (31)	0.90 (0.65-1.24)	0.5173	-
	Whole	59 (18)	0.99 (0.69-1.43)	0.9621	-
	Middle	70 (21)	0.94 (0.67-1.33)	0.7395	-
Grade	Well differentiated	1 (0)	-	-	-
	Moderately differentiated	70 (21)	0.38 (0.05-2.73)	0.3338	-
	Poorly differentiated	234 (72)	0.48 (0.07-3.43)	0.4642	-
	Undifferentiated	18 (6)	0.57 (0.07-4.31)	0.5843	-
Tumor size	Unknown	4 (1)	0.41 (0.04-4.55)	0.4687	-
	≤ 5cm	117 (36)	-	-	-
	> 5cm	145 (44)	1.33 (1.02-1.75)	0.0379	-
T stage	Unknown	65 (20)	0.98 (0.66-1.46)	0.9322	-
	T2	24 (7)	-	-	-
	T3	163 (50)	2.18 (1.17-4.05)	0.0135	-
	T4a	96 (29)	2.90 (1.54-5.45)	0.0009	-
N stage	T4b	44 (13)	4.86 (2.48-9.53)	< 0.0001	-
	N0	38 (12)	-	-	-
	N1	261 (80)	1.47 (0.99-2.20)	0.0588	-
	N2	15 (5)	1.98 (0.95-4.11)	0.0666	-
Node status	N3	13 (4)	1.90 (0.94-3.84)	0.0731	-
	N-	38 (12)	-	-	-
AJCC7 group ¹	N+	289 (88)	1.51 (1.01-2.25)	0.0449	-
	II	187 (57)	-	-	-
	III	140 (43)	1.79 (1.39-2.30)	< 0.0001	1.81 (1.41-2.33) < 0.0001

¹Included in multivariate model. AJCC: American joint commission on cancer; Chemo: Chemotherapy.

selection bias. Surgical techniques and chemotherapy options have drastically changed over time. Therefore, resectability criteria have changed in that time period as well. Given the 18-year time period in our study, selection bias could play a role in neoadjuvant chemotherapy determination, surgical resectability criteria used, and adjuvant chemotherapy recommendations. However, we cannot determine in this retrospective study whether these biases would skew the results in any direction. To account for this, we limited our study to patients with Stage II and Stage III disease given that, in general, they are likely to have resectable disease. Stage I disease was omitted as Stage I patients routinely did not receive chemotherapy. The staging information in the CSP database is based on pathologic staging at the time of surgery. Therefore, we acknowledge that downstaging and decreased tumor burden could have occurred in the neoadjuvant chemotherapy group. However, to limit the potential bias of downstaging disease stage in the cohort that received neoadjuvant chemotherapy, Stage I and IV disease was omitted from our analysis. In particular, Stage I disease should be treated with surgery first, potentially followed with adjuvant chemotherapy. As such, patients who were documented to have Stage I disease and received neoad-

juvant chemotherapy were more likely to have had downstaging of disease.

Another limitation is that although the CSP database provides coding for the receipt of chemotherapy and the first date of chemotherapy, we do not have data on the exact chemotherapy regimen (the type of chemotherapy, number of cycles, dose reductions, *etc.*) or on the successful completion of chemotherapy. Therefore, patients who did have preoperative chemotherapy determined by the first date of surgery could have also received postoperative chemotherapy.

Although the neoadjuvant cohort is smaller than the adjuvant group, our data does not appear underpowered. Prior to the study, a power calculation was performed. Assuming 80% power with a 2-sided log-rank alpha of 0.05 and based on the parameter estimates for neoadjuvant and adjuvant survival in stage II patients at 1 year (83% *vs* 77%, respectively), it would take a sample size of 699 patients in each group to find these differences statistically significant. This however, assumes that the 1 year survival curves (neoadjuvant *vs* adjuvant) are parallel and do not cross. Given that the survivals do cross (Figure 1), and due to the fact that the 3 year and 5 year results showing adjuvant survival is longer than neoadjuvant sur-

vival, a larger sample size would not change our overall conclusion.

As the management of gastric cancer continues to evolve, many questions remain unanswered. The extent of surgical resection, choice of adjunct therapy, and timing of therapy remain under debate. In this study, we compared survival following postoperative and preoperative chemotherapy, with similar outcomes observed between the preoperative and postoperative chemotherapy regimens. On the basis of these observations, we propose that a randomized, controlled trial be conducted to define the optimal timing of chemotherapy administration in the management of surgically resectable gastric cancer.

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COMMENTS

Background

Gastric adenocarcinoma is cancer of the stomach. The outcome of patients diagnosed with gastric cancer is determined by stage of disease. Though surgery remains the best curative-intent treatment, recurrence rates are unfortunately high. Multiple studies have evaluated the benefit of surgery alone or combined with chemotherapy, but there are few studies evaluating the timing of chemotherapy around surgery.

Research frontiers

Multimodality therapies are now being investigated for the treatment of gastric cancer, such as chemoradiation and intraperitoneal chemotherapy; yet these therapies are not standard of care.

Innovations and breakthroughs

The mainstay of treatment is surgical resection either with perioperative chemotherapy or postoperative chemotherapy. Most chemotherapy regimens are either 5-fluorouracil (5-FU) based or cisplatin/oxaliplatin based. Asian studies have also shown benefit with adjuvant S-1, an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on a biochemical modulation of 5-FU.

Applications

This study indicates that chemotherapy and surgery provides the best survival benefits for patients with gastric cancer. There was no difference in survival when comparing neoadjuvant chemotherapy to adjuvant chemotherapy alone.

Terminology

Gastric adenocarcinoma: a cancer of the stomach; Neoadjuvant chemotherapy: chemotherapy given prior to surgical resection; Adjuvant chemotherapy: chemotherapy given after surgical resection.

Peer review

The authors investigated outcomes for patients with gastric cancer treated with surgery and chemotherapy using a population-based cancer registry ($n = 327$). They demonstrated that both chemotherapy and surgical resection are critically important treatment modalities, while reporting no difference in overall survival between patients given neoadjuvant chemotherapy or adjuvant chemotherapy.

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