Original Article

Predictors of outcomes in patients with gastric cancer treated with contemporary multimodality strategies—a single institution experience

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: While gastric cancer is a leading cause of cancer-related mortality in Eastern Europe and Asia, it is less common in the United States. Recommendations regarding optimal treatment of non-metastatic gastric cancer with regard to type and extent of surgery, choice and sequence of chemotherapeutic agents, and use of radiation therapy vary somewhat depending on geographic location. There is paucity in the literature for direct comparison of various practices. To determine how variability in treatment practices affects patient outcomes, we conducted a retrospective study in patients with gastric cancer who had multimodality treatment for non-metastatic gastric cancer.

Methods: We gathered clinical data (patient demographics, pathology reports, type of surgical intervention, chemotherapy, and radiation therapy) for patients diagnosed with gastric adenocarcinoma who underwent gastrectomy at five sites from 2010–2017 using Electronic Health Records and California Cancer Registry databases. Medical chart reviews were conducted to validate patient outcomes. We performed multivariate Cox regression analyses to determine predictors for cancer recurrence and survival. We also performed logistic regression analyses to determine predictors of positive resection margins and hospitalization.

Results: One hundred and sixteen patients met eligibility criteria to be included. Mean age was 65.7± 11.6 years. About 65.5% were male. The most common ethnicities were Asian (44.0%) and Caucasian (37.9%). About 58.6% of the patients had localized disease (defined as pT1–3, pN0) and the remaining 41.4% had loco-regional disease (i.e., pT4 or pN+). About 41.4% of the tumors were diffuse, 27.6% intestinal, 12.0% mixed, and 19.0% unknown histology. Surgery included laparoscopic (94.8%) and open gastrectomy (5.2%). Chemotherapy and radiation therapy were given in 51.7% and 19.0% of the patients, respectively. After a median follow-up time of 19 months after gastrectomy, 16.4% of patients had recurrence and 19.8% had died. Patients who had loco-regional tumors were more likely to have recurrence and death than those who had localized tumors (hazard ratios =7.0, P=0.0228 for recurrence and hazard ratios =3.3, P=0.0160 for death). Positive resection margins were seen in 9% of the patients and were associated with diffuse histology (odds ratio =6.6, P=0.0207). Hospitalization within six months of gastrectomy was seen in 22% of the patients. Peri-operative chemotherapy was the only significant predictor for re-hospitalization (odds ratio =3.5, P=0.0415).

Conclusions: In this contemporary cohort of patients with localized gastric cancer, only the pathological stage was significantly associated with survival while positive resection margins were associated with diffuse histology. Closer monitoring of patients undergoing perioperative chemotherapy within 6 months of surgery is warranted based on our observation of higher rate of re-hospitalization.

Keywords: Gastric cancer; prognostic factors; gastrectomy; multimodality treatment

Submitted Oct 30, 2018. Accepted for publication Jan 11, 2019.
doi: 10.21037/jgo.2019.01.08
View this article at: http://dx.doi.org/10.21037/jgo.2019.01.08

Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide (1). While gastric cancer is a leading cause of cancer-related mortality in Eastern Europe and Asia, it is less common in the United States. Recommendations regarding optimal treatment of non-metastatic gastric cancer with regard to type and extent of surgery, choice and sequence of chemotherapeutic agents, and use of radiation therapy vary somewhat depending on geographic location. In the U.S., until recently adjuvant chemo-radiation with fluoropyrimidines was most commonly used based on the INT0116 trial (2), while in Europe a perioperative approach (3) is favored and in East Asia patients mostly are treated with adjuvant chemotherapy alone (4). Also, there is heterogeneity and lack of consents regarding the optimal extent for lymph node dissection during gastrectomy (5-7). There is a paucity of literature concerning the direct comparison of various practices since most pivotal trials compared multimodality treatment to surgery alone (1-4). More recently, the FLOT-4 trial showed superior outcomes with a taxane containing perioperative triplet chemotherapy regimen compared to the anthracycline containing regimen established in the MAGIC trial (8). However, trials directly comparing chemotherapy alone to an intensified regimen on chemotherapy and radiation have been negative so far (9-11). To determine how variability in treatment practices affects patient outcomes, we conducted a retrospective study in patients with gastric cancer treated at five University of California (UC) medical centers. Here we present the results from one center.

Methods

Study cohort

This study was approved by the Institutional Review Board at the University of California in Irvine prior to the collection of data (approval #11846). The study cohort which was retrospectively identified from electronic databases included patients diagnosed with gastric or gastro-esophageal adenocarcinoma who underwent gastrectomy at one center from 2010–2017.

Data collection

We gathered retrospective data from UC electronic health records and California Cancer Registry databases. UC electronic health records and California Cancer Registry data were linked by patient identifiers in order to obtain more complete information about patients' treatment and follow-up. The UC electronic health records included demographics (age, race/ethnicity, and gender), diagnosis (ICD-9, ICD-10), procedure codes (ICD-10, CPT), laboratory tests and results, drugs, outpatient visits, and inpatient admissions. The California Cancer Registry data included tumor characteristics (stage, histology), surgical characteristics (technique, lymph node recovery), and chemotherapy characteristics (administration, regimens, completion status). We conducted chart reviews to validate patient outcomes.

Statistical methods

Descriptive statistics such as percentage, mean, and standard deviation were used to summarize patient demographic, clinical, tumor, surgical, and chemotherapy characteristics. To determine significant predictors of patient outcomes, only variables which temporally preceded the outcomes were included in the regression models as predictors. First, we performed univariate regression analyses in which one independent variable was included in the regression model at a time. Then we performed multivariate regression analyses in which we included the predictors that was found to be statistically significant at P value <0.05 in the univariate analyses. Correlations among the predictors were assessed before being considered in the multivariate analyses.

Cox regression models with proportional hazard distribution were performed to determine the predictors of cancer recurrence and death. The unit of analysis was a patient. The dependent variable was the time from gastrectomy to cancer recurrence (or death). For patients who had never had recurrence (or death) or were lost to follow up, the time was censored by their last visit. The independent variables included patient demographic, clinical, tumor, surgical, and chemotherapy characteristics. Hazard ratio was used to determine significant predictors at

significance level <5%. A hazard ratio of value greater than 1 indicated that one group of patients was at greater risk of recurrence (or death) than the other group; a hazard ratio of value less than 1 indicated lower risk; and a hazard ratio of value equal to 1 indicated equal risk.

Logistic regression models were used to determine predictors of positive resection margins and hospitalization. The unit of analysis was a patient. The dependent variable was an indicator whether a patient had positive resection margins (or hospitalization within 6 months after gastrectomy). The independent variables included patient demographic, clinical, tumor, surgical, and chemotherapy characteristics. Odds ratio was used to determine significant predictors of hospitalization at significance level <5%.

Results

Patient demographic, clinical, tumor, chemotherapy, radiation therapy, and surgical characteristics are shown in *Table 1*.

Demographic characteristics

One hundred and sixteen patients fulfilled eligibility and were included. Their age at diagnosis ranged from 26 to 88 years, with the mean of 65.7 years (SD=11.6). About 65.5% were male. The most common ethnicities were Asian (44.0%) and Caucasian (37.9%).

Clinical characteristics

About 43.1% of the patients smoked or drank alcohol on a regular basis; 7.8% experienced significant weight loss at the time of cancer diagnosis; 8.6% had a history of cancer other than gastric cancer; and 55.2% of the patients had at least one comorbidity.

Tumor characteristics

Anatomical location

About 31.9% of the tumors were located in the esophagus and junction; 47.4% in the stomach body; and 20.7% in the antrum, pylori, and duodenum.

Pathological stage

About 41.4% were locoregional (i.e., pT4 or pN1+) while 58.6% were localized (i.e., pT1–3 and pN0).

Tumor size

About 40.5% of the tumors were small (<2 cm); 27.6% were medium (2–4 cm); 21.6% were large (>4 cm); and 10.3% of the tumors had missing size. The larger the tumor size, the higher the T and N stages (P=0.0068).

Histology

About 41.4% of the tumors were diffuse; 27.6% were intestinal; 12.0% were mixed type; and 19.0% were unknown histology. Diffuse histology were more common among tumors located in the stomach than in the esophagus (52.0% *vs.* 19.0%, P=0.0008) and more prevalent among tumors with pT4 than pT1–3 (80.0% *vs.* 40.0%, P=0.0140).

Chemotherapy and radiation therapy

About 51.7% of the patients received chemotherapy. Among the chemotherapy recipients, about 26.7% received neoadjuvant only, 38.3% received adjuvant only, and 35.0% received perioperative chemotherapy. Only 65.0% completed their required chemotherapy courses. Last but not least, about 19.0% of the patients received radiation therapy.

Surgery

Gastrectomy included laparoscopic (94.8%) and open surgery (5.2%). Total gastrectomy was performed in 12.9% of the patients, more frequently in higher stages: 4% of pT1, 0% in pT2, 23% in pT3, and 50% in pT4 (P<0.0001). About 24.1% of the gastrectomy cases had <15 recovered lymph nodes; 52.6% had 15–29 recovered lymph nodes; and 23.3% had 30+ recovered lymph nodes.

Outcomes

Clinical outcomes are summarized in *Table 2*.

Predictors of cancer recurrence

After a median follow-up time of 19 months after gastrectomy, 16% of patients had cancer recurrence. *Table 3* shows the predictors of cancer recurrence. In univariate analysis, we found several significant predictors of cancer recurrence which included race (non-Asian *vs.* Asian: hazard ratio HR =4.3, 95% CI: 1.3–14.9, P=0.0196), significant weight loss (yes *vs.* no: HR =5.2, 95% CI: 1.7–16.0, P=0.0038), pathological stage (loco-regional *vs.* localized stage: HR =10.8,

Table 1 Demographic, clinical, tumor, chemotherapy, radiation, and surgical characteristics

Variables	Descriptive statistics (N=116)
Demographics	
Age at diagnosis, mean ± SD [range] (years)	65.7±11.6 [26–88]
Sex (%)	
Male	65.5
Female	34.5
Race/ethnicity (%)	
Asian	44.0
Caucasian	37.9
Hispanic	15.5
African American	0.9
Others	1.7
Clinical characteristics	
Smoking/alcohol (%)	
Yes	43.1
No or unknown	56.9
Significant weight loss (%)	
Yes	7.8
No or unknown	92.2
History of cancer (%)	
Yes	8.6
No or unknown	91.4
Number of comorbidities (%)	
0	44.8
1–2	19.0
3+	36.2
Tumor characteristics	
Anatomic location (%)	
Esophagus/Junction	31.9
Stomach body	47.4
Antrum/pylori/duodenum	20.7
pT stage (%)	
1	44.8
2	16.4
3	30.2
4	8.6
pN stage (%)	
0	61.2
1	21.5
2	6.9
3	10.3
Pathological stage (%)	
Loco-regional (pT4 or pN1+)	41.4
Localized (pT1–3 & pN0)	58.6
Tumor size (%)	
Small (<2 cm)	40.5
Medium (2–4 cm)	27.6
Large (>4 cm)	21.6
Missing data	10.3
Cell type (%)	
Diffuse	41.4
Intestinal	27.6
Mixed	12.0
Unknown	19.0
Diffuse histology by anatomical location (%)	
Esophagus	19.0
Stomach	52.0
Diffuse histology by T stage (%)	
pT4	80.0
pT1–3	40.0
Chemotherapy	
Receipt of chemotherapy (%)	
Yes	51.7
No	48.3

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Descriptive statistics (N=116)
Administration among chemotherapy receivers (n=60) (%)	
Neoadjuvant only	26.7
Adjuvant only	38.3
Perioperative	35.0
Agents among chemotherapy receivers (n=60) (%)	
Multi-agent	86.7
Single agent	13.3
Completion status among chemotherapy receivers (n=60) (%)	
Completed	65.0
In progress/not completed	35.0
Radiation therapy	
Receipt of radiation therapy (%)	
Yes	19.0
No	81.0
Surgery	
Surgical technology (%)	
Open	5.2
Laparoscopic	94.8
Surgical type (%)	
Total	12.9
Partial	87.1
Number of recovered lymph nodes (%)	
<15	24.1
15–29	52.6
30+	23.3

95% CI: 3.1–37.3, P=0.0002), resection margin (positive *vs.* negative: HR =3.3, 95% CI: 1.1–9.9, P=0.0363), surgery type (total *vs.* partial: HR =6.6, 95% CI: 2.1–21.0, P=0.0014), and perioperative chemotherapy (perioperative *vs.* none: HR =15.0, 95% CI: 3.1–71.9, P=0.0007). However, in multivariate analysis, the only significant predictor of cancer recurrence was pathological stage (loco-regional *vs.* localized stage: HR =7.0, 95% CI: 1.3–37.1, P=0.0228).

Table 2 Outcomes

Variables	Descriptive statistics (N=116)
Primary outcomes	
Cancer recurrence* (%)	
Distant recurrence	12.1
Local recurrence	4.3
None	83.6
Death* (%)	
Dead	19.8
Alive	80.2
Secondary outcomes	
Positive resection margins (%)	
Yes	8.6
No	91.4
Hospital admission within 6 months after gastrectomy (%)	
Yes	21.6
No	78.4
Number of admissions per patient	
Mean ± SD	1.4±0.8
Median [range]	1 [1–4]
Total length of stay (days)	
Mean ± SD	10.2±14.7
Median [range]	7 [1–74]

*, with a median follow-up time of 19 months after gastrectomy.

Predictors of death

After a median follow-up time of 19 months after gastrectomy, 20% of patients had died. *Table 4* shows the predictors of death. In multivariate analysis, the only significant predictors of death were pathological stage (loco-regional *vs.* localized stage: HR =3.3, 95% CI: 1.3–8.6, P=0.0160).

Predictors of positive resection margins

Positive resection margins were seen in 9% of the patients. *Table 5* shows the predictors of positive resection margins. Histology was the only significant predictor of positive resection margins: patients who had tumors with diffuse

Table 3 Predictors of cancer recurrence

Predictors	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Demographics				
Age at diagnosis (65+ *vs.* younger)	0.7 (0.3–1.8)	0.4830		
Sex (male *vs.* female)	0.8 (0.3–2.0)	0.6134		
Race (non-Asian *vs.* Asian)	4.3 (1.3–14.9)	0.0196	3.3 (0.8–12.6)	0.0822
Clinical characteristics				
Smoking/alcohol (yes *vs.* no)	1.6 (0.6–4.0)	0.2988		
Significant weight loss (yes *vs.* no/unknown)	5.2 (1.7–16.0)	0.0038	2.2 (0.7–7.6)	0.2013
History of cancer (yes *vs.* no)	3.5 (0.8–16.2)	0.1043		
Number of comorbidities (1+ *vs.* none)	1.2 (0.5–3.3)	0.7667		
Tumor characteristics				
Anatomical location (esophagus *vs.* stomach)	1.3 (0.5–3.3)	0.5663		
Pathological stage (loco-regional *vs.* localized)	10.8 (3.1–37.3)	0.0002	7.0 (1.3–37.1)	0.0228
Tumor size (large *vs.* small/med/unknown)	2.4 (0.9–6.4)	0.0795		
Cell type (diffuse *vs.* intestinal/unknown)	2.2 (0.9–5.5)	0.0874		
Surgery				
Resection margin (Positive *vs.* Negative)	3.3 (1.1–9.9)	0.0363	1.6 (0.5–5.1)	0.4627
Number of recovered lymph nodes (<15 *vs.* 15+)	1.8 (0.5–4.6)	0.2046		
Surgical type (total *vs.* partial)	6.6 (2.1–21.0)	0.0014	2.4 (0.7–8.4)	0.1639
Chemotherapy				
Perioperative *vs.* none	15.0 (3.1–71.9)	0.0007	2.2 (0.3–17.0)	0.4393
Perioperative *vs.* neoadjuvant alone	3.0 (0.6–14.4)	0.1635		
Perioperative *vs.* adjuvant alone	2.2 (0.8–6.1)	0.1439		

histology were 6.6 times more likely to have positive resection margins than patients with intestinal, mixed, or unknown histology (OR =6.6, 95% CI: 1.3–32.6, P=0.0207).

Predictors of hospitalization

Hospitalization within 6 months of gastrectomy was seen in 22% of the patients with a mean length of stay of 10 (±15 days). *Table 6* shows the predictors of hospitalizations. Perioperative chemotherapy was the only significant predictor of re-hospitalization within 6 months after gastrectomy. Patients who received perioperative chemotherapy were 3.5 times more likely to be re-hospitalized than those without chemotherapy (OR =3.5, 95% CI: 1.0–11.7, P=0.0415).

Discussion

The aim of the current single institution study was to determine prognostic factors for patients with non-metastatic gastric cancer treated with modern multi-modality regimens. We observed that there was little

Table 4 Predictors of death

Predictors	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Demographics				
Age at diagnosis (65+ *vs.* younger)	2.2 (0.8–6.0)	0.1156		
Sex (male *vs.* female)	0.7 (0.3–1.7)	0.4346		
Race (non-Asian *vs.* Asian)	2.8 (1.1–7.7)	0.0377	1.5 (0.5–4.4)	0.4799
Clinical characteristics				
Smoking/alcohol (yes *vs.* no)	1.1 (0.5–2.4)	0.9018		
Significant weight loss (yes *vs.* no/unknown)	5.5 (2.2–13.4)	0.0002	2.3 (0.8–6.7)	0.1258
History of cancer (yes *vs.* no)	5.5 (1.5–19.9)	0.0093	2.7 (0.6–12.6)	0.2038
Number of comorbidities (1+ *vs.* none)	1.1 (0.5–2.5)	0.8850		
Tumor characteristics				
Anatomical location (esophagus *vs.* stomach)	2.3 (1.0–5.2)	0.0471	3.0 (1.0–8.8)	0.0852
Pathological stage (loco-regional *vs.* localized)	4.5 (1.8–10.9)	0.0011	3.3 (1.3–8.6)	0.0160
Tumor size (large *vs.* small/med/unknown)	3.4 (1.4–7.9)	0.0049	1.5 (0.5–5.1)	0.4896
Cell type (diffuse *vs.* intestinal/unknown)	0.9 (0.4–2.2)	0.8778		
Surgery				
Resection margin (positive *vs.* negative)	2.0 (0.6–6.8)	0.2580		
Number of recovered lymph nodes (<15 *vs.* 15+)	0.9 (0.3–2.5)	0.7618		
Surgical type (total *vs.* partial)	6.1 (2.4–15.5)	0.0002	3.1 (1.0–9.9)	0.0559
Chemotherapy				
Perioperative *vs.* none	2.2 (0.8–6.2)	0.1495		
Perioperative *vs.* neoadjuvant alone	0.9 (0.2–3.1)	0.8472		
Perioperative *vs.* adjuvant alone	2.2 (0.6–8.0)	0.2187		

variation in surgical technique since the majority of patients underwent laparoscopic gastrectomy performed by one surgeon. However, there was some variation in chemotherapy administration with similar numbers of patients receiving neoadjuvant, adjuvant, and perioperative chemotherapy.

Despite a heterogeneous population with a range of different demographics and tumor characteristics, the only significant predictor of recurrence and death in multivariate analysis was the pathologic stage. Our findings are consistent with available literature highlighting the prognostic significance of pathologic stage in resected gastric cancer (12,13). Importantly, the observed correlation between tumor extent and survival was dichotomous; that is, the hazard ratios for recurrence and death did not increase gradually with increasing TNM stage, as previously shown (14), but appeared to solely distinguish loco-regional stages (pT4, pN1+) from localized stages (pT1–3, pN0).

Our cohort included a higher proportion of poorly differentiated diffuse type adenocarcinomas compared to previous reports in the literature (12-16). These cases were associated with higher rates of positive resection margins,

Table 5 Predictors of positive resection margins

Predictors	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Demographics				
Age at diagnosis (65+ *vs.* younger)	0.6 (0.2–2.1)	0.4149		
Sex (male *vs.* female)	1.3 (0.3–5.1)	0.7554		
Race (non-Asian *vs.* Asian)	1.9 (0.5–7.9)	0.3588		
Clinical characteristics				
Smoking/alcohol (yes *vs.* no)	0.5 (0.1–2.2)	0.3874		
Significant weight loss (yes *vs.* no/unknown)	1.4 (0.2–12.1)	0.7824		
History of cancer (yes *vs.* no)	1.2 (0.1–10.6)	0.8710		
Number of comorbidities (1+ *vs.* none)	1.2 (0.3–4.7)	0.7485		
Tumor characteristics				
Anatomical location (esophagus *vs.* stomach)	1.5 (0.4–5.6)	0.5671		
Pathological stage (loco-regional *vs.* localized)	1.4 (0.3–6.3)	0.6547		
Pathological stage (unknown *vs.* localized)	3.0 (0.5–17.9)	0.2236		
Tumor size (large *vs.* small/med/unknown)	0.9 (0.2–4.5)	0.9007		
Cell type (diffuse *vs.* intestinal/mixed/unknown)	6.6 (1.3–32.6)	0.0207	6.6 (1.3–32.6)	0.0207
Chemotherapy				
Neoadjuvant (yes *vs.* no)	1.3 (0.3–5.6)	0.7383		

confirming available data (16). However, this did not translate into a decreased survival, potentially due to the cytotoxic effect of adjuvant chemotherapy (17).

With regards to adverse events associated with treatment, we found that patients who received perioperative chemotherapy were three times more likely to be hospitalized than those without chemotherapy. While survival does not appear to be negatively impacted, minimizing re-hospitalization would positively affect patients' quality of life but also significantly reduce health care associated costs. Thus, based on our data, closer monitoring of patients undergoing perioperative chemotherapy within 6 months of surgery could be warranted.

The limitations of this study include retrospective nature, relatively small sample size, and single institution data. On the other hand, the data is derived from a contemporary patient cohort and thus might be more generalizable to current practices. The fact that we focused on a single institution with the majority gastrectomies done in a uniform fashion allowed us to minimize confounding factors in our analysis of prognostic factors. Also, the empirical effects of the significant predictors are large, with the hazard ratios and odds ratios of magnitudes from 3 to 7.

Next steps would include validation of our findings in independent cohorts, including sites with higher variability in surgical approach (e.g., D1 versus D2 resection, etc.) to test whether surgical technique might compensate for some of the observation made in this current study. Finally, it would be interesting to integrate molecular data to the clinical variables to improve the performance of available prognostic factors for survival after surgery.

Table 6 Predictors of hospitalization

Predictors	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Demographics				
Age at diagnosis (65+ *vs.* younger)	0.7 (0.3–1.8)	0.4811		
Sex (male *vs.* female)	0.9 (0.4–2.3)	0.8570		
Race (non-Asian *vs.* Asian)	1.9 (0.7–4.9)	0.1775		
Clinical characteristics				
Smoking/alcohol (yes *vs.* no)	1.3 (0.5–3.1)	0.5772		
Significant weight loss (yes *vs.* no/unknown)	1.0 (0.2–5.4)	0.9594		
History of cancer (yes *vs.* no)	0.9 (0.2–4.5)	0.9007		
Number of comorbidities (1+ *vs.* none)	1.6 (0.6–4.0)	0.3186		
Tumor characteristics				
Anatomical location (esophagus *vs.* stomach)	2.4 (1.0–6.1)	0.0550		
Pathological stage (loco-regional *vs.* localized)	1.4 (0.6–3.4)	0.4490		
Tumor size (large *vs.* small/med/unknown)	0.6 (0.2–2.1)	0.4487		
Cell type (diffuse *vs.* intestinal/unknown)	1.1 (0.5–2.8)	0.7640		
Surgery				
Resection margin (positive *vs.* negative)	1.6 (0.4–6.8)	0.5002		
Number of recovered lymph nodes (<15 *vs.* 15+)	0.8 (0.3–2.1)	0.6110		
Surgical type (total *vs.* partial)	1.4 (0.4–4.8)	0.6068		
Chemotherapy				
Perioperative *vs.* none	3.5 (1.0–11.7)	0.0415	3.5 (1.0–11.7)	0.0415
Perioperative *vs.* neoadjuvant alone	3.2 (0.8–11.9)	0.0859		
Perioperative *vs.* adjuvant alone	2.5 (0.7–8.4)	0.1469		

Acknowledgements

The authors thank Ms. Liz Adams, cancer registry manager at UCI Chao Family Comprehensive Cancer Center, who provided data and expertise that greatly assisted the research. *Funding:* This work was partially supported by grant UL1 TR001414 from the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through the Biostatistics, Epidemiology and Research Design Unit. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo.2019.01.08). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board at the University

of California in Irvine prior to the collection of data (approval # 11846).

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Cite this article as: Hoang T, Park M, Hiyama D, Dayyani F. Predictors of outcomes in patients with gastric cancer treated with contemporary multimodality strategies—a single institution experience. J Gastrointest Oncol 2020;11(2):411-420. doi: 10.21037/jgo.2019.01.08

