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Improving the quality of gastric cancer surgery: factors associated with positive resection margins for gastrectomy

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Abstract

Purpose: Positive margins after gastrectomy have been associated with poor patient prognosis. This study aimed to identify risk factors associated with margin-positive resections.

Methods: The National Cancer Database was queried from 2004 to 2014 for all patients with gastric adenocarcinoma who underwent resection with curative intent and had known margin status. Univariable and multivariable logistic regression analysis was performed to identify variables associated with positive margins.

Results: A total of 32,193 patients were identified who met study inclusion criteria, of which 11.8% (3786 patients) had a margin-positive resection. Tumor size > 6 cm, T3 or T4 tumors, tumor location in the body of stomach or in multiple regions, signet ring cell histology, presence of lymphovascular invasion, positive lymph node involvement, and lack of neoadjuvant therapy were independently associated with an increased risk of positive margins.

Conclusions: Advanced disease characteristics, aggressive tumor pathology, and absence of neoadjuvant therapy were associated with margin-positive resections.

Keywords: Gastric cancer, Resection margin, National Cancer Database

1 Introduction

Gastric cancer is the fifth most commonly occurring cancer and has become the third leading cause of cancer-related deaths worldwide [1, 2]. Curative-intent surgery (margin-negative resection with D2 lymph node dissection) in combination with chemotherapy/chemoradiation therapy remains the only hope for cure. As gastric cancer may spread at the level of submucosa, an additional length (5–6 cm) of grossly normal tissue is often resected to maximize the likelihood of achieving a microscopically negative resection margin [3, 4]. Despite the aggressive resection, margin-positive rates of up to 20% have been reported in patients after gastrectomy [5–8]. The occurrence of a margin-positive resection (R1) has been identified as an independent predictor of poor prognosis, particularly among patients with early-stage gastric cancer [7–13]. Patients with positive resection margins continue to have a high rate of both local and distant recurrences even if they receive aggressive adjuvant multimodality therapy [14].

Currently, the National Comprehensive Cancer Network (NCCN) practice guidelines recommend neoadjuvant treatment for cancers of the esophagus and gastroesophageal junction, and this treatment algorithm is also being explored in other solid tumors, including rectal, pancreas, and breast cancers, to facilitate margin-negative resections- [15–20]. Initial investigational studies in patients with locally advanced gastric cancer have also demonstrated promising results for the use of neoadjuvant therapies, with the potential to reduce the incidence of R1 resections as well as improve recurrence-

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free (RFS) and overall survival [21–23]. Neoadjuvant therapy may also enhance local disease control which is the most common pattern of recurrence in gastric cancer patients [19, 24–27]. Thus, it is important to identify patients with a high risk of R1 resection and recommend them for preoperative chemotherapy or chemoradiation therapy with hopes of improving their overall outcomes.

In this context, the objective of this study was to use the National Cancer Database (NCDB) to identify risk factors associated with R1 resections in gastric cancer patients.

2 Methods

2.1 Patient selection

This was a retrospective, population-based study using data provided by NCDB. The NCDB is a collaborative program between the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. The NCDB gathers data from over 1500 CoC-accredited cancer hospitals and represents 70% of newly diagnosed cancer cases in the United States [28].

The NCDB was queried between 2004 and 2014 for all patients ≥18 years of age with invasive gastric adenocarcinoma who underwent elective partial or total gastrectomy with curative intent and had available margin status data. Patients were excluded from this study if they had a diagnosis of a second malignancy during their lifetime, metastatic disease, a palliative resection, an emergent resection, or missing/unknown margin status. A resection was defined as emergent if the number of days between diagnosis and surgery was recorded as < 1 day. A palliative resection was defined in NCDB as a surgical procedure, which may include a bypass procedure, performed to alleviate symptoms but not to treat the primary tumor. Disease staging was performed using pathologically-determined tumor size, extension, and nodal involvement in accordance with the American Joint Committee on Cancer (AJCC) Staging System, 7th

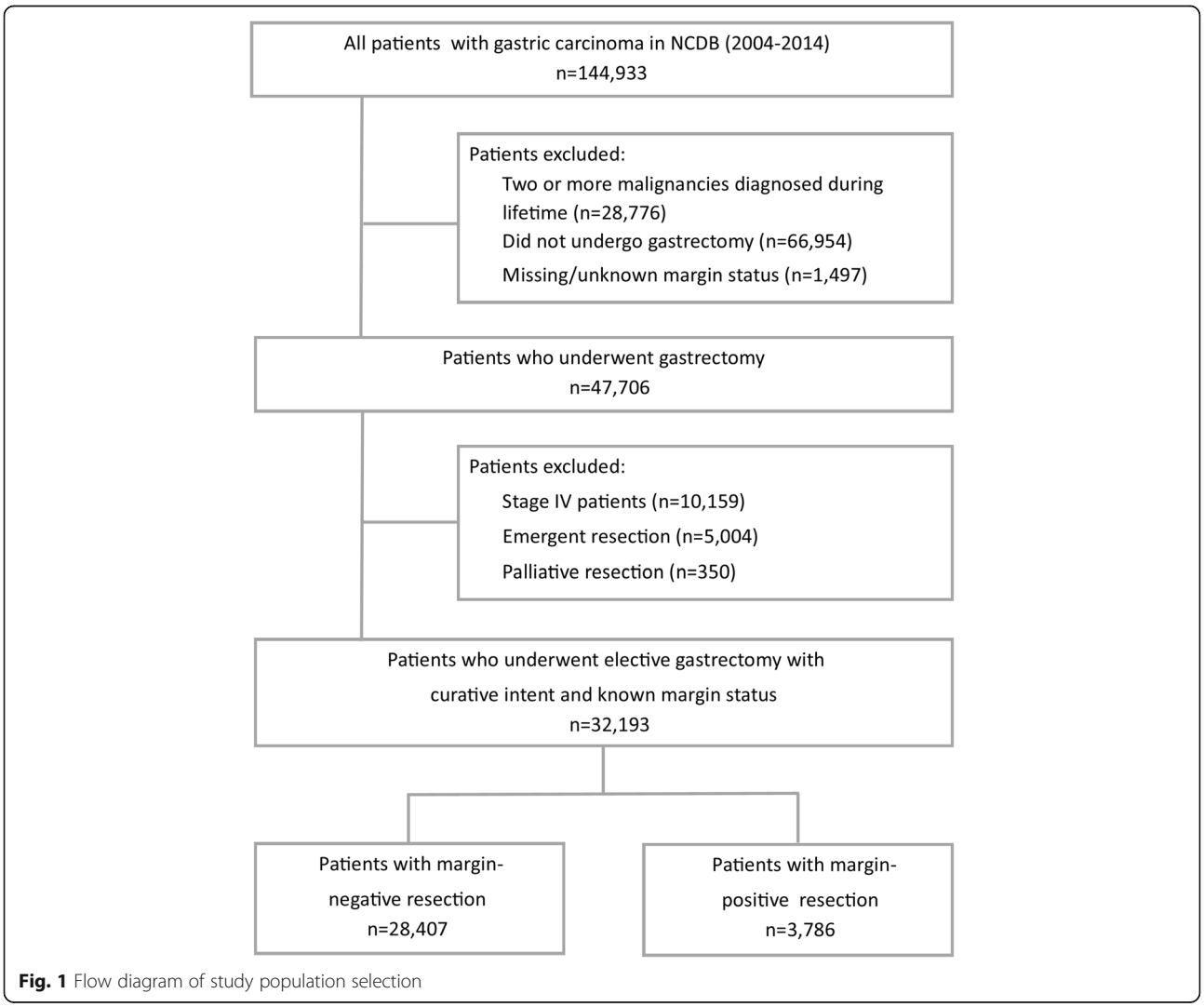

Fig. 1 Flow diagram of study population selection

edition [29]. The flow diagram of the study population selection is depicted in Fig. 1. To ensure that the exclusion of patients with missing/unknown margin status does not introduce potential bias to this study, patient demographics and presenting characteristics were compared between patients with known margin status and those with missing/unknown margin status (Supplemental Table 1).

2.2 Statistical analysis

Patient demographics, disease and treatment characteristics, and post-operative and long-term outcomes were abstracted from NCDB for patients meeting study inclusion criteria. Univariable logistic regression analysis using available patient demographics and disease characteristics data was performed to identify variables associated with a margin-positive resection. Significant variables on univariable analysis were selected for inclusion in multivariable analysis. Overall survival (OS) was defined as the time from the date of surgery to the date of death or last contact as recorded in the NCDB. Survival estimates were generated using Kaplan–Meier method and compared using the log-rank test. Univariable Cox proportional hazard regression analysis was performed using available patient demographics and disease characteristics data to identify variables associated with OS. An adjusted Cox proportional hazard regression analysis was performed to evaluate margin-positive resection as an independent prognostic factor. A p-value < 0.05 was considered significant. Statistical analysis were performed using SPSS (Version 22, SPSS Inc., Chicago, IL, USA). This study was approved by the Partners Health Research Committee institutional review board.

3 Results

3.1 Patient characteristics

A total of 32,193 patients were identified from NCDB who met study inclusion criteria. Patient demographics and disease characteristics are summarized in Table 1. The annual rate of margin-positive resections remained consistent throughout the years captured in this study, ranging from 10.9% to 13.7%. The most of patients (28,407, 88.2%) had a margin-negative resection, while 11.8% (3786 patients) had a margin-positive resection.

3.2 Univariable and multivariable logistic analysis for positive resection margin

On univariable analysis, patient factors associated with margin-positive resections included younger age ($p = 0.002$), female sex ($p = 0.003$), white or black race compared to Asian ($p = 0.001–0.004$), and a higher Charlson-Deyo comorbidity index (CDCI) ($p = 0.004$) (Table 2). Histologically, patients with margin-positive resections were more likely to have tumors of larger size ($p < 0.001$), poorly or undifferentiated grade ($p < 0.001$), non-adenocarcinoma histology ($p < 0.001$), higher T, N, and overall stage ($p < 0.001$), location in the stomach body, along the greater curvature of the stomach, or in multiple regions ($p < 0.001–0.003$), and with the presence of lymphovascular invasion ($p < 0.001$). In addition, patients with margin-positive resections were less likely to have received neoadjuvant therapy ($p < 0.001$) and more likely to have undergone total gastrectomy or en block/multivisceral resection (both $p < 0.001$).

On multivariable analysis, tumor size > 6 cm, T3 or T4 tumors, tumor location in the body of the stomach or in multiple regions, signet ring cell histology, presence of lymphovascular invasion, positive lymph node involvement, and lack of neoadjuvant therapy were independently associated with an increased risk of a margin-positive resection (Table 2).

3.3 Positive resection margin is associated with worse survival

Patients with margin-positive resections of all stages had significantly decreased OS compared to those with margin-negative resections (1-year OS: 64% vs. 84%; 3-year OS: 31% vs. 62%; 5-year OS: 25% vs. 55%, all $p < 0.001$) (Fig. 2A). This survival difference persisted when patients were stratified by AJCC stage (5-year OS: 59% vs. 74% for Stage 0-I; 35% vs. 56% for Stage II; 20% vs. 34% for Stage III, all $p < 0.001$) (Fig. 2B-D).

4 Discussion

The presence of residual gastric cancer is a strong predictor of poor prognosis after gastrectomy and an independent risk factor for decreased survival [8, 10, 11]. The association with adverse tumor characteristics suggests that positive margins reflect an underlying aggressive biology of disease. Adjuvant radiation has been shown in clinical trials to provide a survival benefit after gastrectomy; however, patients with positive margins are often excluded from these studies and even aggressive multimodality adjuvant treatment may not be sufficient to overcome the negative prognosis that positive margins portend [14, 30, 31].

Consistent with previous reports, the present study demonstrated the significantly decreased OS in patients with a margin-positive resection compared to those with a margin-negative resection [8, 10, 12]. Positive margins remained an independent predictor of poor prognosis after adjusting for stage and biologic factors.

Regarding clinical features associated with positive surgical margin, younger age, female gender, larger tumor size, poorer tumor differentiation, lymphvascular invasion, neoadjuvant chemotherapy, and more advanced tumor stage were identified as risk factors, which was similar to previous studies [32–34]. In multivariable

Table 1 Patient demographics and disease characteristics

Characteristic	All patients *n* = 32,193	Patients with margin-negative resection *n* = 28,407	Patients with margin-positive resection *n* = 3786
Age, year, mean ± SD	65.3 ± 12.8	65.4 ± 12.8	64.7 ± 13.4
Sex			
Male	20,979 (65.2)	18,595 (88.6)	2384 (11.4)
Female	11,214 (34.8)	9812 (87.5)	1402 (12.5)
Race			
White	23,583 (75.0)	20,764 (88.0)	2819 (12.0)
Black	4758 (15.1)	4186 (88.0)	572 (12.0)
Asian	2975 (9.5)	2680 (90.1)	295 (9.9)
Others	121 (0.5)	110 (90.9)	11 (9.1)
CDCI			
0	21,906 (68.0)	19,295 (88.1)	2611 (11.9)
1	7655 (23.8)	6743 (88.1)	912 (11.9)
≥ 2	2632 (8.2)	2369 (90.0)	263 (10.0)
Tumor Size			
≤ 2 cm	6138 (21.7)	5878 (95.8)	260 (4.2)
2-4 cm	9136 (32.2)	8354 (91.4)	782 (8.6)
4-6 cm	6784 (23.9)	5908 (87.1)	876 (12.9)
> 6 cm	6275 (22.2)	4944 (78.8)	1331 (21.2)
Tumor Differentiation			
Well	1633 (5.4)	1581 (96.8)	52 (3.2)
Moderate	9135 (30.2)	8538 (93.5)	597 (6.5)
Poor	18,851 (62.2)	16,006 (84.9)	2845 (15.1)
Undifferentiated	669 (2.2)	562 (84.0)	107 (16.0)
Tumor Histology			
Adenocarcinoma	24,412 (75.8)	22,043 (90.3)	2369 (9.7)
Mucinous adenocarcinoma	865 (2.7)	745 (86.1)	120 (13.9)
Signet ring cell carcinoma	6060 (18.8)	4878 (80.5)	1182 (19.5)
Others	856 (2.7)	741 (86.6)	115 (13.4)
Tumor Location			
Proximal	12,585 (43.0)	11,321 (90.0)	1264 (10.0)
Body	2409 (8.2)	2150 (89.2)	259 (10.8)
Distal	7950 (27.2)	7046 (88.6)	904 (11.4)
Lesser curve	3003 (10.3)	2712 (90.3)	291 (9.7)
Greater curve	1265 (4.3)	1123 (88.8)	142 (11.2)
Overlapping	2044 (7.0)	1588 (77.7)	456 (22.3)
T Stage			
Tis-T1	7652 (23.8)	7500 (98.0)	152 (2.0)
T2	4583 (14.2)	4423 (96.5)	160 (3.5)
T3	12,461 (38.7)	11,009 (88.3)	1452 (11.7)
T4	7497 (23.3)	5475 (73.0)	2022 (27.0)
N Stage			
N0	14,885 (46.2)	14,199 (95.4)	686 (4.6)

Table 1 Patient demographics and disease characteristics *(Continued)*

Characteristic	All patients *n* = 32,193	Patients with margin-negative resection *n* = 28,407	Patients with margin-positive resection *n* = 3786
N1	6287 (19.5)	5598 (89.0)	689 (11.0)
N2	5617 (17.5)	4678 (83.3)	939 (16.7)
N3	5404 (16.8)	3932 (72.8)	1472 (27.2)
Overall Stage			
Stage 0-I	9634 (29.9)	9467 (98.3)	167 (1.7)
Stage II	11,021 (34.2)	10,140 (92.0)	881 (8.0)
Stage III	11,538 (35.9)	8800 (76.3)	2738 (23.7)
Lymphvascular invasion			
Absent	8000 (56.9)	7466 (93.3)	534 (6.7)
Present	6058 (43.1)	4785 (79.0)	1273 (21.0)
Neoadjuvant therapy			
No	8127 (45.7)	7339 (90.3)	788 (9.7)
Yes	9644 (54.3)	7931 (82.2)	1713 (17.8)
Extent of Resection			
Partial	20,552 (69.6)	18,474 (89.9)	2078 (10.1)
Total	5922 (20.0)	5006 (84.5)	916 (15.5)
En block/Multi-visceral	3069 (10.4)	2565 (83.6)	504 (16.4)
Region of Resection			
Distal	6673 (32.4)	6006 (90.0)	667 (10.0)
Proximal	7184 (34.9)	6514 (90.7)	670 (9.3)
Total	6731 (32.7)	5649 (83.9)	1082 (16.7)

*Results reported as number (%) unless otherwise noted
SD indicates standard deviation; *CDCI* Charlson-Deyo Comorbidity Index, *cm* Centimeter

analyses, only larger tumor size (> 6 cm), signet ring cell histology, deeper tumor infiltration (T3–4 stage), positive lymph node metastasis, lymphovascular invasion, and without using neoadjuvant therapy remained as independent factors for positive surgical margin. The result indicated that aggressive tumor biology might be the main factors contributing to positive surgical margin after gastrectomy. Particularly, poor differentiated tumor cells, like signet ring cell or diffuse type GC cells, may spread subepithelially beyond the macroscopically detectable boundaries of the lesion [35], thus a wider macroscopically free margin cannot predict microscopically negative margins [36]. Though the use of intraoperative frozen section to determine the extent of surgical margin is applied, the rate of R0 resection remains unsatisfied. For one reason, frozen biopsy is time and resource consuming, and is not feasible to be routinely used in every case. For another, like signet ring cell histology, which is characterized by high mucin content, is difficult to be evaluated on hematoxylin-eosin (HE) staining, resulting to false negative in frozen biopsy [37]. Therefore, surgeons should have more discretion when managing those patients.

In studies of cancers of the esophagus and gastroesophageal junction, neoadjuvant therapy has been shown to reduce the likelihood of a margin-positive resection [16, 38]. In the landmark MAGIC trial of patients with resectable gastroesophageal cancer who were randomized to peri-operative chemotherapy and surgery or surgery alone, more patients who received perioperative chemotherapy reached a curative resection [39]. In our study population, not using neoadjuvant therapy was identified as a variable that was associated with the risk of margin-positive resection (OR 2.01, 95% CI 1.84–2.20). As neoadjuvant chemotherapy is a modifiable treatment variable, patients who display several of the other characteristics associated with margin-positive resection can be considered for neoadjuvant treatment to improve their overall outcomes.

Limitations of the present study included the potential selection bias inherent to a retrospective review and the data constraints of using a large, nationwide database. We were not able to differentiate between proximal and distal margin status and a patient was considered to have a margin-positive resection regardless of the location of the positive margin. Detailed information about the neoadjuvant therapy was also not available. However,

Table 2 Logistic regression analysis of patient and treatment characteristics associated with margin-positive resection

	Univariable		**Multivariable**	
Characteristic	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (per 1 SD)	0.996 (0.993–0.998)	**0.002**	1.00 (0.990–1.006)	0.66
Sex (Ref: Male)				
Female	1.12 (1.039–1.196)	**0.003**	1.02 (0.825–1.251)	0.88
Race (Ref: Asian)				
White	1.23 (1.087–1.400)	**0.001**	1.02 (0.740–1.411)	0.90
Black	1.24 (1.070–1.440)	**0.004**	0.93 (0.639–1.365)	0.72
Other	0.91 (0.483–1.708)	0.77	0.59 (0.074–4.751)	0.62
CDCI (Ref: 0)				
1	1.00 (0.922–1.083)	0.99	1.12 (0.904–1.392)	0.30
≥ 2	0.82 (0.718–0.938)	**0.004**	1.18 (0.806–1.721)	0.40
Tumor Size (Ref: ≤2 cm)				
2-4 cm	2.12 (1.832–2.445)	**< 0.001**	0.98 (0.665–1.455)	0.94
4-6 cm	3.35 (2.905–3.868)	**< 0.001**	1.24 (0.836–1.841)	0.28
> 6 cm	6.09 (5.301–6.988)	**< 0.001**	1.75 (1.181–2.592)	**0.01**
Tumor Differentiation (Ref: Well)				
Moderate	2.13 (1.593–2.837)	**< 0.001**	1.20 (0.532–2.710)	0.66
Poor	5.40 (4.088–7.144)	**< 0.001**	1.59 (0.715–3.553)	0.25
Undifferentiated	5.79 (4.100–8.174)	**< 0.001**	1.20 (0.422–3.402)	0.74
Tumor Histology (Ref: Adenocarcinoma)				
Mucinous adenocarcinoma	1.45 (1.230–1.826)	**< 0.001**	1.09 (0.628–1.901)	0.75
Signet ring cell carcinoma	2.26 (2.089–2.434)	**< 0.001**	1.30 (1.032–1.641)	**0.03**
Other	1.44 (1.181–1.765)	**< 0.001**	1.67 (0.930–2.999)	0.09
Tumor Location (Ref: Proximal)				
Body	1.15 (1.050–1.258)	**0.003**	2.03 (1.372–2.998)	**< 0.001**
Distal	1.08 (0.937–1.243)	0.29	1.27 (0.854–1.882)	0.24
Lesser curve	0.96 (0.840–1.099)	0.56	0.93 (0.586–1.486)	0.77
Greater curve	1.13 (0.942–1.361)	0.19	0.84 (0.447–1.590)	0.60
Overlapping	2.57 (2.283–2.898)	**< 0.001**	2.01 (1.302–3.106)	**0.002**
T Stage (Ref: Tis-T1)				
T2	1.79 (1.425–2.235)	**< 0.001**	1.89 (0.836–4.273)	0.126
T3	6.51 (5.492–7.711)	**< 0.001**	3.92 (1.898–8.099)	**< 0.001**
T4	18.22 (15.397–21.567)	**< 0.001**	11.06 (5.293–23.124)	**< 0.001**
N Stage (Ref: N0)				
N1	2.55 (2.282–2.844)	**< 0.001**	1.97 (1.433–2.721)	**< 0.001**
N2	4.16 (3.745–4.609)	**< 0.001**	2.34 (1.696–3.221)	**< 0.001**
N3	7.75 (7.031–8.540)	**< 0.001**	2.80 (2.029–3.869)	**< 0.001**
Overall Stage (Ref: Stage I)			–	–
Stage II	4.93 (4.165–5.825)	**< 0.001**		
Stage III	17.64 (15.047–20.675)	**< 0.001**		
Lymphvascular invasion (Ref: Absent)				
Present	3.72 (3.341–4.141)	**< 0.001**	1.45 (1.166–1.815)	**0.001**
Neoadjuvant therapy (Ref: Yes)				
No	2.01 (1.838–2.201)	**< 0.001**	1.26 (1.020–1.550)	**0.03**

Table 2 Logistic regression analysis of patient and treatment characteristics associated with margin-positive resection *(Continued)*

	Univariable		Multivariable	
Extent of Resection (Ref: Partial)			–	–
Total	1.63 (1.496–1.769)	**< 0.001**		
En bloc/Multi-visceral	1.75 (1.572–1.942)	**< 0.001**		
Region of Resection (Ref: Proximal)				
Distal	1.08 (0.965–1.209)	0.18	0.82 (0.604–1.103)	0.19
Total	1.86 (1.680–2.064)	**< 0.001**	1.09 (0.853–1.381)	0.51

*Bold denotes significant *p*-value
OR indicates odds ratio, *CI* Confidence interval, *CDCI* Charlson-Deyo Comorbidity Index, *cm* Centimeter

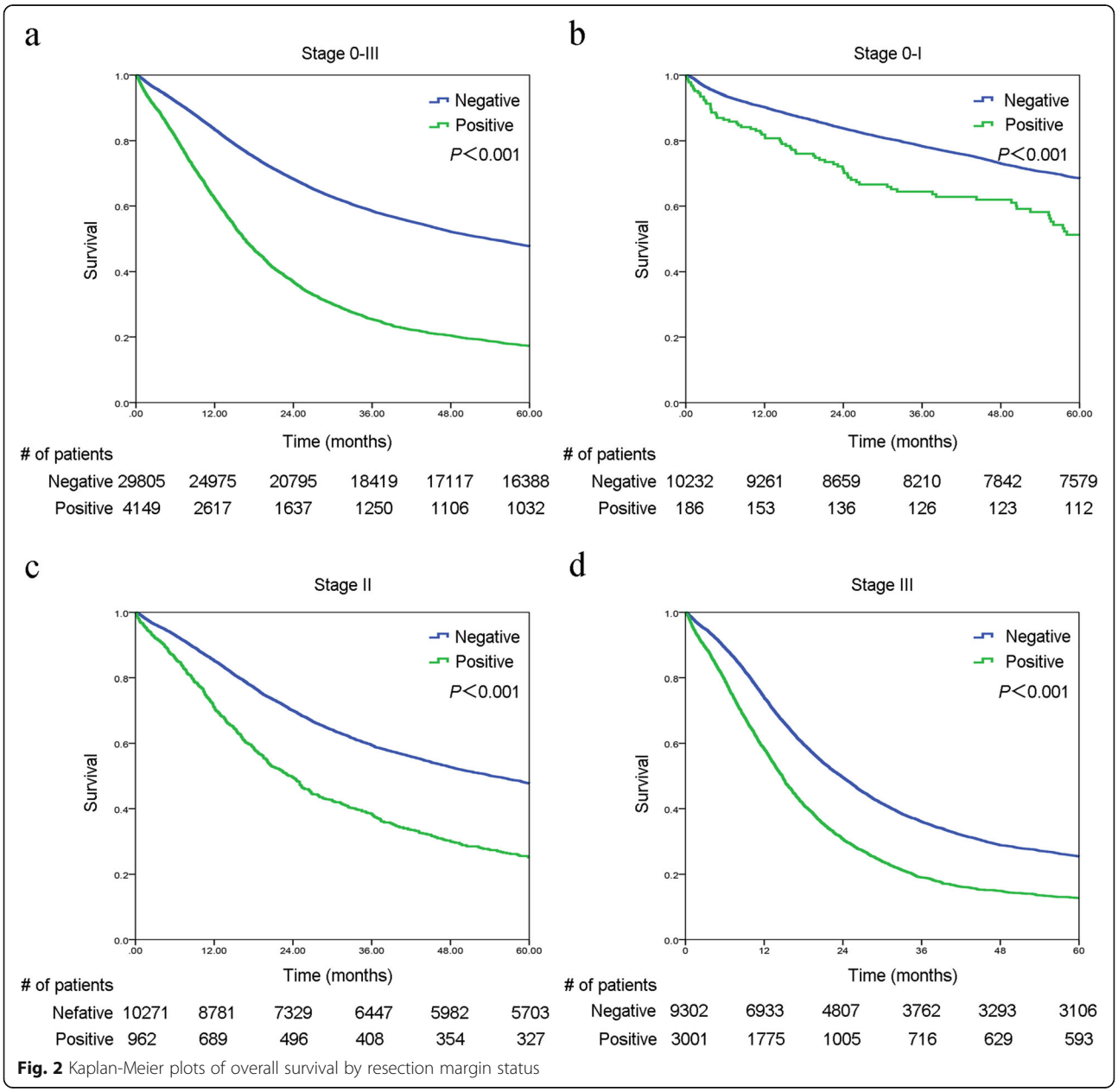

Fig. 2 Kaplan-Meier plots of overall survival by resection margin status

despite the loss of some clinical granularity, the NCDB is a representative collection of 70% of diagnosed cancer cases in the United States. The NCDB also does not provide additional information on facility volume, which may impact patient treatment, including use of neoadjuvant therapy, and subsequent outcomes.

5 Conclusions

Positive margins are an independent predictor of poor survival in gastric cancer. Identification of associated characteristics can aid in the risk stratification of patients who have increased likelihood of a margin-positive resection and allow for appropriate treatment planning including neoadjuvant chemotherapy or chemoradiation therapy with the hopes of improving patients' long-term outcomes.

6 Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44178-022-00001-0.

Additional file 1.

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None.

Authors' contributions

Study design: XF Wang, YH Sun; Data acquisition: JJ Zhao, HJ Li; Data analysis and interpretation: JJ Zhao, HJ Li, Y Fang; Statistical analysis: JJ Zhao, HJ Li; Manuscript preparation: JJ Zhao, HJ Li, Y Fang; Manuscript editing: XF Wang, YH Sun; Manuscript review: XF Wang, YH Sun. The authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by thes authors.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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