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Should Signet Ring Cell Histology Alter the Treatment Approach for Clinical Stage I Gastric Cancer?

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Abstract

Background.—Surgery alone is standard-of-care for stage I gastric adenocarcinoma; however, clinicians can offer preoperative therapy for clinical stage I disease with signet ring cell histology, given its presumed aggressive biology. We aimed to assess the validity of this practice.

Methods.—The National Cancer Database (2004–2015) was reviewed for patients with clinical stage I signet ring cell gastric adenocarcinoma who underwent treatment with surgery alone, perioperative chemotherapy, neoadjuvant therapy, or adjuvant therapy. Analysis was stratified by preoperative clinical/pathologic stage. Primary outcome was overall survival (OS).

Results.—Of 1018 patients, median age was 60 years (± 14); 53% received surgery alone ($n = 542$), 5% received perioperative chemotherapy ($n = 47$), 12% received neoadjuvant therapy ($n = 125$), and 30% received adjuvant therapy ($n = 304$). For clinical stage I disease, surgery alone was associated with an improved 5-year OS rate (71%) versus perioperative chemotherapy (58%), neoadjuvant therapy (38%), or adjuvant therapy (52%) [overall $p < 0.01$]. For pathologic stage I, surgery alone had equivalent or improved survival compared with perioperative, neoadjuvant, and adjuvant therapy (5-year OS: 78% vs. 89% [$p = 0.77$] vs. 64% [$p = 0.04$] vs. 84% [$p = 0.99$]). Adjuvant therapy was associated with improved 5-year OS compared with pretreatment for those patients upstaged (37%) to pathologic stage II/III (55% vs. 36% and 34% vs. 7%; all $p < 0.01$).

Conclusions.—This stage-specific study demonstrates improved survival with surgery alone for clinical stage I signet ring cell gastric adenocarcinoma. Despite 37% of clinical stage I patients

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being upstaged to pathologic stage II/III, adjuvant therapy offers a favorable rescue strategy, with improved outcomes compared with those treated preoperatively. Surgery alone also affords similar or improved survival for pathologic stage I disease versus multimodality therapy. This study challenges the bias to overtreat stage I signet ring cell gastric adenocarcinoma.

As the sixth most common cancer worldwide, gastric adenocarcinoma imposes a significant disease burden, with the highest incidence evident in Eastern Asia, Europe, and South America.^{1,2} In the US, there are over 22,000 new cases each year.³ Despite the overall decreased incidence of gastric adenocarcinoma in recent decades, the proportion of cases with signet ring cell histology is steadily rising, comprising approximately 35–40%.^{4,5}

There is an increasing body of evidence that supports the prognostic significance of distinct tumor histologies in gastric adenocarcinoma.⁶ Historically, the Lauren classification was widely used to distinguish intestinal types from diffuse types.⁷ However, given the heterogeneity of the disease, histopathologic examination is necessary to better inform management decisions and long-term outcomes. In 2010, the World Health Organization provided a more detailed schema that includes tubular, papillary, mucinous, poorly cohesive, and mixed histology, with signet ring cell carcinoma considered a poorly cohesive subtype.⁶

The prognosis of signet ring cell gastric adenocarcinoma remains controversial as some retrospective studies have suggested no difference in long-term outcomes compared with other histologic variants, while others suggest worse outcomes.^{8,9} Signet ring cell histology represents poorly differentiated tumors that are typically associated with more advanced disease.¹ When considering all stages, 5-year overall survival (OS) was 51% for signet ring cell histology, compared with 76% for well-differentiated and moderately differentiated tumors.⁴ This trend of signet ring cell histology harboring a worse prognosis is consistent with most reported data.^{10,11}

Upfront resection with negative margins is considered standard-of-care treatment for early-stage disease. However, current National Comprehensive Cancer Network (NCCN) guidelines do not individualize management based on histology, and recommend surgical resection for localized clinical stage I disease, specifically for T1a or T1b tumors.¹² Given the potentially more aggressive biologic behavior associated with signet ring cell histology, a common clinical practice pattern is to pursue multimodality therapy, specifically with preoperative chemotherapy, even for clinical stage I disease.

Established treatment paradigms include upfront surgery followed by adjuvant systemic therapy or chemoradiation, or perioperative chemotherapy, based on the results of the CLASSIC, Intergroup-0116, MAGIC, and FLOT-4 clinical trials^{13–17} Despite the fact that surgery alone is standard-of-care for stage I gastric adenocarcinoma, there is discordance between existing guidelines and current practice paradigms. Many clinicians offer preoperative chemotherapy for clinical stage I disease with signet ring cell histology, given its presumed aggressive biology. Our primary aim was to assess the validity of this practice by comparing outcomes of different treatment approaches, including surgery alone, perioperative chemotherapy, neoadjuvant therapy, and adjuvant therapy, specifically for clinical stage I signet ring cell gastric adenocarcinoma.

METHODS

Data Source

Patients were retrospectively identified from the National Cancer Database (NCDB), a clinical oncology registry sponsored by the American College of Surgeons and the American Cancer Society, which includes data from over 1500 Commission on Cancer facilities.¹⁸ The database was queried to include patients with primary clinical stage I gastric adenocarcinoma with signet ring histology who underwent curative-intent resection from 2004 to 2015. The International Classification for Diseases, Third Revision (ICD-3) code 8490 for signet ring cell histology was used to extract only patients with this confirmed histology. Patients with missing clinical stage, pathologic stage, unknown treatment sequence, or insufficient follow-up time (< 6 months per the 'landmark method') were excluded.¹⁹

Study Variables

Given patient clinicopathologic data spanned the American Joint Committee on Cancer (AJCC) 6th and 7th editions, patients were re-coded based on contemporary AJCC 8th edition criteria. Treatment was classified as surgery alone, perioperative chemotherapy, neoadjuvant therapy, or adjuvant therapy as defined by the treatment-surgery sequence codes within the NCDB. Neoadjuvant therapy was defined as receiving chemotherapy, radiation therapy, or chemoradiation prior to surgery, while adjuvant therapy included chemotherapy, radiation therapy, or chemoradiation after surgery. For analysis of clinical stage I patients who were upstaged to pathologic stage II or III after resection, pretreatment was defined as having received neoadjuvant therapy or perioperative chemotherapy, and adjuvant therapy was defined as having received any therapy after curative-intent surgery. The Charlson–Deyo score was divided into three categories (0, 1, and 2+). Tumor grade was classified as well/moderately differentiated or poorly differentiated/anaplastic, and margin status was classified as either R0 (negative microscopic margins) or R1/R2 (positive microscopic or macroscopic margins).

Survival Analysis and Outcomes

Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).²⁰ Statistical significance was defined as $p < 0.05$ for two-tailed tests. Descriptive statistics for each variable were reported. Patients were allocated into four treatment groups (surgery, perioperative chemotherapy, neoadjuvant therapy, adjuvant therapy). A Chi-square test or Fisher's exact test was performed for discrete variables, and analysis of variance (ANOVA) or the Kruskal–Wallis test was used for continuous variables. Kaplan–Meier analysis and pairwise comparisons with Tukey–Kramer correction were performed for the four treatment groups for clinical stage I patients who were pathologic stage I and for patients who received surgery alone, pretreatment, or adjuvant therapy for clinical stage I patients who were upstaged to pathologic stage II or stage III. OS was calculated as the time from diagnosis to the date of death or date of last available follow-up. Concordance between clinical and pathologic stage was assessed for all clinical stage I patients, clinical stage I patients who were pathologic stage I, and clinical stage I patients who were upstaged to pathologic stage II or III. Five-year OS rate estimates were reported.

RESULTS

Demographic and Clinicopathologic Characteristics

Of the 202,216 patients in the NCDB who had gastric cancer, 1018 had clinical stage I tumors with signet ring cell histology (Fig. 1). The demographic and clinicopathologic data are listed in Table 1. The mean age at diagnosis was 60 years (± 14). Fifty-three percent of patients were female ($n = 545$); the majority of patients were White (71%, $n = 725$); 53% ($n = 542$) underwent surgery alone; 5% ($n = 47$) received perioperative chemotherapy; 12% ($n = 125$) received neoadjuvant therapy; and 30% ($n = 304$) received adjuvant therapy. The majority of patients had a Charlson–Deyo score of 0 (68%, $n = 693$). 64% ($n = 650$) of patients had T1 disease and 36% ($n = 368$) had T2 disease. Mean tumor size was 3 ± 3 cm.

Patients who received perioperative chemotherapy were younger (52 ± 12 years), compared with those who underwent surgery alone (63 ± 14 years), neoadjuvant therapy (60 ± 12 years), and adjuvant therapy (58 ± 13 years) [$p < 0.01$]. More male patients (60%, $n = 75$) comprised the neoadjuvant therapy cohort compared with the other treatment groups ($p < 0.01$). A higher proportion of patients who received perioperative chemotherapy and neoadjuvant therapy had T2 disease (64%, $n = 30$; 66%, $n = 82$) compared with those who underwent surgery alone (23%, $n = 122$) [$p < 0.01$]. Mean tumor size for the surgery alone cohort was smaller (2 ± 2 cm) compared with that of the perioperative chemotherapy (4 ± 5 cm), neoadjuvant therapy (4 ± 4 cm), and adjuvant therapy (4 ± 3 cm) cohorts ($p < 0.01$). The majority of patients received an R0 resection (91%, $n = 922$), with surgery alone patients having the highest R0 resection rate (96%, $n = 515$; $p < 0.01$) (Table 1). A higher proportion of patients in the adjuvant therapy cohort (54%) had evidence of lymphovascular invasion (LVI) compared with the other treatment groups (surgery alone: 13%; perioperative chemotherapy: 30%; neoadjuvant therapy: 27%; $p < 0.01$). Median follow-up for all patients was 36 months (1–139), and median follow-up for surgery alone, perioperative chemotherapy, neoadjuvant therapy, and adjuvant therapy was 41 (1–139), 34 (6–120), 22 (5–120), and 31 (3–123) months, respectively.

Survival Analysis

For *clinical* stage I disease ($n = 1018$), surgery alone was associated with an improved 5-year OS rate (71%) when compared with perioperative chemotherapy (58%), neoadjuvant therapy (38%), or adjuvant therapy (52%) [all $p < 0.01$ on pairwise comparison] (Fig. 2a).

For *pathologic* stage I disease ($n = 675$), surgery alone had an equivalent 5-year OS rate as perioperative chemotherapy and adjuvant therapy (78% vs. 89% [$p = 0.77$] vs. 84% [$p = 0.99$], on pairwise comparison) (Fig. 2b). Compared with patients who received only neoadjuvant therapy, those who received surgery alone had improved 5-year OS (78% vs. 64%; $p = 0.04$).

Adjuvant therapy was associated with an improved 5-year OS rate compared with pretreatment (neoadjuvant and perioperative therapy) for those upstaged to *pathologic* stage II or stage III disease (Fig. 3). For *pathologic* stage II disease, 5-year OS was 37% for surgery alone, 36% for pretreatment ($p = 0.55$ on pairwise comparison), and 55% for adjuvant therapy ($p = 0.03$ on pairwise comparison) (Fig. 3a). For *pathologic* stage III

disease, 5-year OS was 25% for surgery alone, 7% for pretreatment ($p = 0.06$ on pairwise comparison), and 34% for adjuvant therapy ($p = 0.18$ on pairwise comparison) (Fig. 3b).

Concordance

For all clinical stage I patients, concordance between clinical and pathologic stage I was 58% ($n = 588$) (Fig. 4a). Thirty-nine percent ($n = 402$) of clinical stage I patients were upstaged, with pathologic stage II, III, and IV comprising 18% ($n = 187$), 19% ($n = 190$), and 2% ($n = 25$) of patients, respectively. Among patients who received surgery alone, concordance between clinical and pathologic stage I was 83% ($n = 449$) (Fig. 4b). Only 15% ($n = 79$) were upstaged. Specifically, 8% ($n = 44$) were pathologic stage II, 6% ($n = 32$) were pathologic stage III, and $< 1\%$ ($n = 3$) were pathologic stage IV. For patients who received preoperative therapy (neoadjuvant or perioperative therapy), concordance between clinical and pathologic stage I was 33% ($n = 57$) (Fig. 4c). A total of 59% ($n = 101$) were upstaged to pathologic stage II (29%, $n = 50$), stage III (25%, $n = 42$), and stage IV (5%, $n = 9$). Eight percent ($n = 14$) of patients who received preoperative therapy achieved a complete pathologic response.

DISCUSSION

Signet ring cell histology is considered an aggressive subtype of gastric adenocarcinoma that may warrant the use of multimodality therapy to potentially aid with tumor downstaging and improved rates of margin-negative resection.²¹ However, variable reports on stage-specific survival and a paucity of data supporting a particular therapeutic approach highlight the fact that the management of stage I signet ring cell gastric cancer remains controversial. Thus, a stage- and histology-specific treatment paradigm needs to be defined. For clinical stage I gastric adenocarcinoma with signet ring cell histology, this study supports pursuing a surgery-first strategy (5-year OS: surgery alone 71% vs. perioperative chemotherapy 58% vs. neoadjuvant therapy 38% vs. adjuvant therapy 52%; all $p < 0.01$). For patients with concordant pathologic stage I disease after resection, surgery alone was associated with equivalent or improved 5-year OS compared with multimodal therapy (surgery alone: 78% vs. perioperative chemotherapy 89% [$p = 0.77$] vs. neoadjuvant therapy 64% [$p = 0.04$] vs. adjuvant therapy 84% [$p = 0.99$]). Importantly, for clinical stage I patients who were pathologically upstaged to either stage II or stage III disease, adjuvant therapy offered a viable rescue therapy. For pathologic stage II disease, surgery alone, preoperative therapy, and adjuvant therapy had a 5-year OS of 37%, 36%, and 55%, respectively, and for pathologic stage III disease, 5-year OS was 25%, 7%, and 34%, respectively. Even in patients who do not recover well enough after surgery to receive adjuvant therapy, patients who underwent surgery alone demonstrated equivalent or improved survival compared with those who received preoperative treatment.

The impact of signet ring cell histology on long-term outcomes remains a point of contention. Gronnier et al. reported signet ring cell morphology was not a negative prognostic indicator.²² A more recent retrospective review of 769 patients by Kwon and colleagues corroborated these findings, demonstrating no survival difference between histologic subtypes for early-stage gastric cancer.²³ On the contrary, the presence of signet

ring cells has been shown by other investigators to be a poor prognostic factor, even when present in early gastric cancer, occurring at a mean age of 55 years, which on average is 8 years earlier than patients with non-signet ring cell gastric cancer typically present.²³ In addition, Piessen et al. reported signet ring cell histology was associated with higher rates of peritoneal carcinomatosis, lymph node invasion, lower R0 resection rates, and earlier recurrence.²⁴ Worse survival with signet ring cell histology has been attributed to its chemoresistant behavior.^{25,26} Given that multimodality therapy may prove relatively ineffective, our analyses support adherence to current NCCN guidelines that recommend upfront resection for clinical stage I disease, even in the presence of signet ring cell histology.

In this unique patient population, there is a clear need to better identify the optimal treatment strategy while avoiding unnecessary morbidity and mortality. A neoadjuvant approach for locally advanced gastric cancer was largely based on the seminal MAGIC trial, which demonstrated improved 5-year OS of 36% versus 23% compared with surgery alone (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.6–0.93; $p < 0.01$).¹⁴ Importantly, this study included only T2 or higher disease and cannot be applied to T1 disease with or without lymph node involvement. In addition, no histologic data were available and only 49.5% of patients received the full perioperative regimen. More recently, Al-Batran and colleagues reported the benefit of perioperative fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT-4) over epirubicin and cisplatin plus either fluorouracil or capecitabine, with a median survival of 50 vs. 35 months (HR 0.77, 95% CI 0.63–0.94; $p = 0.01$).¹⁷ Although this effect was pronounced in intestinal type tumors, it is worth noting 28% of patients in the study had signet ring cell histology. All had clinical T2 or higher disease, positive lymph nodes, or both. Despite these study limitations, data from these trials are often extrapolated to patients with early-stage signet ring cell carcinoma.

Notably, in a retrospective review of 1050 patients with non-metastatic signet ring cell gastric cancer, of whom 19.5% ($n = 180$) had clinical stage I disease, Messenger et al. reported that the administration of perioperative chemotherapy with epirubicin/cisplatin/5-fluorouracil (ECF) or cisplatin/5-fluorouracil (CF) had no benefit with regard to tumor downstaging, decreasing the nodal disease burden, or R0 resection rates compared with upfront surgery. In fact, receiving perioperative chemotherapy was an independent predictor for worse median survival (12.8 vs. 14 months; HR 1.4, 95% CI 1.1–1.9; $p = 0.04$).²⁷ The authors attribute the limited efficacy of chemotherapy to an absence of cytotoxic and cytostatic effects with this histology. Additionally, Heger et al. demonstrated that for patients who received neoadjuvant chemotherapy, signet ring cell histology was associated with a decreased incidence of pathologic response (21 vs. 34%; $p < 0.01$) and worse median survival (26 vs. 47 months; $p < 0.01$) when compared with non-signet ring cell histology.¹ In our study cohort, for patients with T2 tumors, 64% ($n = 30$) received perioperative chemotherapy and 66% ($n = 82$) received neoadjuvant therapy, compared with 23% ($n = 122$) who underwent surgery alone. These data highlight the concern with clinicians overtreating patients with stage I disease who have signet ring cell histology. The ongoing, prospective, randomized, phase II/III PRO-DIGE-19 trial is currently investigating the benefit of ECF perioperative chemotherapy compared with surgery and adjuvant

chemotherapy for stage Ib–III signet ring cell gastric cancer, the results of which are eagerly awaited (NCT01717924).²⁸

Similar to neoadjuvant strategies, there are limited data to support adjuvant therapy specifically for signet ring cell histology. In the phase III CLASSIC trial, patients with stage II–IIIb gastric cancer with all histologies were randomized to receive adjuvant capecitabine and oxaliplatin after D2 gastrectomy or surgery alone. Three-year disease-free survival (DFS) and OS were improved in the treatment arm compared with the control arm (DFS: 74% vs. 59%, $p<0.01$; OS: 83% vs. 78%, $p<0.05$).^{15,16} In addition, the Intergroup-0116 trial findings demonstrated the benefit of adjuvant chemoradiation for non-metastatic stage Ib–IV gastric cancer. Patients in the treatment arm had improved median OS (36 vs. 27 months; HR 1.35, 95% CI 1.09–1.66; $p<0.01$), although a limitation of the study is that a D2 lymphadenectomy was performed on only 10% of patients. Again, while these studies did not comment on histologic data, adjuvant regimens have been broadly applied to clinical stage I signet ring cell gastric cancer.

In this study, the inferior survival observed in clinical stage I signet ring gastric adenocarcinoma patients who received multimodality therapy may be attributable to the associated morbidity of chemotherapy agents in a histology that is inherently less chemosensitive. Interestingly, while the clinical and pathologic correlation of stage I disease was 58% for patients who underwent surgery-first, the concordance decreased to only 33% for those who received preoperative therapy. Multimodality therapy with limited efficacy may ultimately delay definitive surgical treatment, resulting in disease progression, which is manifested as a higher proportion of pretreatment patients who were pathologically upstaged and had evidence of LVI, compared with patients who received surgery alone. While it is possible that a delay in surgery from receiving relatively ineffective chemotherapy partly explains the greater incidence of finding pathologic stage II and III disease at resection, it is most likely a consequence of selection bias that we are unable to definitively characterize in this retrospective study that led those patients to be administered preoperative therapy. However, it is important to note that even in the upstaged cohort, adjuvant therapy was associated with improved survival compared with preoperative therapy, again supporting a surgery-first paradigm in patients with clinical stage I disease.

Beyond the chemoresistance profile, neoadjuvant therapies may also lead to the worsening of performance status, especially in patients who are frailer. While performance status or frailty indices were not available in the NCDB, it is important to note a higher proportion of patients in the surgery-alone cohort had Charlson–Deyo scores ≥ 2 compared with the other treatment groups. Thus, improved performance status does not explain the improved survival observed in the surgery-alone group compared with the other multimodal treatment strategies.

This study supports a surgery-first approach for clinical stage I patients with signet ring cell histology. Even in pathologically upstaged patients, adjuvant therapy offers a valid approach with favorable results. In the absence of a clear survival benefit, clinicians should be cautious with using preoperative therapy for clinical stage I signet ring cell gastric adenocarcinoma. While multidisciplinary tumor boards may opt for more aggressive

treatment regimens for younger patients with no evidence of comorbid disease, the findings of this study warrant careful consideration.

Limitations of this study include its retrospective design, which is vulnerable to misclassification bias and missing data. Second, the NCDB does not contain data for specific variables of interest, such as signet cell histology classification (pure, predominant, or partial), disease-specific survival, the chemotherapy regimens used, duration of chemotherapy, and extent of lymphadenectomy. Third, the study time period included the use of the AJCC 6th and 7th editions. Although all patients were re-coded to the most recent AJCC 8th edition, those with missing data were excluded, which lends itself to potential selection bias.

CONCLUSIONS

Our stage-specific study demonstrates improved 5-year OS for patients who undergo surgery alone for clinical stage I signet ring cell gastric adenocarcinoma. For concordant pathologic stage I disease, surgery alone offers equivalent survival outcomes when compared with multimodality therapy. Even for patients who were upstaged to stage II or III on final pathology, adjuvant therapy provides a favorable rescue strategy, evidenced by the improvement in survival seen when compared with upstaged patients who were treated preoperatively. This study ultimately challenges the intrinsic bias to overtreat stage I signet ring cell gastric adenocarcinoma, and supports a surgery-first approach for these patients.

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FIG. 1.
Exclusion and inclusion criteria for population of interest. *NCDB* National Cancer Database

FIG. 2.
Overall survival for **a** clinical stage I patients by treatment type, and **b** pathologic stage I patients by treatment type, up to 60 months from diagnosis

FIG. 3.
Overall survival for **a** clinical stage I patients upstaged to pathologic stage II, and **b** clinical stage I patients upstaged to pathologic stage III, up to 60 months from diagnosis

FIG. 4.
Concordance of clinical stage I with final pathologic stage for **a** all clinical stage I patients;
b surgery-first patients; and **c** preoperative therapy patients

TABLE 1

Clinicopathologic characteristics of clinical stage I patients, by treatment modality

Variable	All patients [n = 1018 (%)]	Surgery alone [n = 542 (53)]	Perioperative chemotherapy [n = 47 (5)]	Neoadjuvant therapy [n = 125 (12)]	Adjuvant therapy [n = 304 (30)]	p-Value
Age at diagnosis, years (mean ± SD)	60 ± 14	63 ± 14	52 ± 12	60 ± 12	58 ± 13	<0.01
Sex						
Male	473 (47)	224 (41)	22 (47)	75 (60)	152 (50)	<0.01
Female	545 (53)	318 (59)	25 (53)	50 (40)	152 (50)	
Race						
White	725 (71)	387 (71)	33 (70)	94 (75)	211 (69)	0.16
Black	126 (13)	72 (13)	4 (8)	15 (12)	35 (12)	
Asian	134 (13)	68 (13)	5 (11)	11 (9)	50 (16)	
Other	33 (3)	15 (3)	5 (11)	5 (4)	8 (3)	
Insurance status						
Not insured	35	18 (3)	1 (2)	3 (2)	13 (4)	<0.01
Private	457	217 (41)	24 (51)	53 (43)	163 (54)	
Government	516	302 (56)	22 (47)	67 (55)	125 (42)	
Charlson–Deyo score						
0	693 (68)	342 (63)	37 (79)	93 (74)	221 (73)	<0.01
1	231 (23)	135 (25)	9 (19)	27 (22)	60 (20)	
2+	94 (9)	65 (12)	1 (2)	5 (4)	23 (7)	
T-stage (AJCC 8th edition)						
T1	650 (64)	420 (77)	17 (36)	43 (34)	170 (56)	<0.01
T2	368 (36)	122 (23)	30 (64)	82 (66)	134 (44)	
Tumor grade						
Well/moderate	31 (3)	19 (4)	0 (0)	4 (4)	8 (3)	0.73
Poor/anaplastic	909 (97)	481 (96)	39 (100)	110 (96)	279 (97)	
Tumor size, cm (mean ± SD)	3 ± 3	2 ± 2	4 ± 5	4 ± 4	4 ± 3	<0.01
Lymphovascular invasion	210 (30)	53 (13)	11 (30)	25 (27)	121 (54)	<0.01
Margin						
R0	922 (91)	515 (96)	39 (87)	108 (89)	260 (86)	<0.01

Variable	All patients [<i>n</i> = 1018 (%)]	Surgery alone [<i>n</i> = 542 (53)]	Perioperative chemotherapy [<i>n</i> = 47 (5)]	Neoadjuvant therapy [<i>n</i> = 125 (12)]	Adjuvant therapy [<i>n</i> = 304 (30)]	<i>p</i> -Value
R1/R2	93 (9)	21 (4)	6 (13)	14 (11)	42 (14)	
Follow-up, months (median)	36 (1–139)	41 (1–139)	34 (6–120)	22 (5–120)	31 (3–123)	< 0.01

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *AJCC* American Joint Committee on Cancer