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ORIGINAL ARTICLE

Prognostic impact of surgery after chemotherapy for type 4 gastric cancer

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Abstract

Purpose To assess the clinical indications for, and prognostic impact of surgery after, chemotherapy for type 4 gastric cancer.

Methods The subjects of this retrospective study were 67 patients who received chemotherapy for type 4 gastric cancer. The patients were grouped into those with progressive disease (PD group) and those without PD (non-PD group), according to the tumor response to chemotherapy.

Results Distant metastases developed in 58 patients. With regard to tumor response, there were 16 patients in the PD group and 51 patients in the non-PD group. The prognosis of the PD group patients was significantly poorer than that of the non-PD group patients ($p < 0.0001$). R0 resection was performed for 21 of 23 patients who underwent surgery after chemotherapy. Multivariate analysis revealed tumor response and surgery as independent prognostic factors ($p = 0.0001$ and $p = 0.0009$, respectively). Moreover, multivariate analysis of the surgery group revealed that metastatic nodal status (N0-1 vs. N2-3) and residual tumor status (R0 vs. R1-2) were significant independent prognostic factors ($p = 0.0258$ and $p = 0.0458$, respectively).

Conclusion The findings of this study suggest that surgery after chemotherapy for type 4 gastric cancer may improve the prognosis of responders with N0-1 status, who undergo curative R0 resection.

Keywords Gastric cancer · Type 4 · Chemotherapy · Surgery · Prognosis

Introduction

The incidence of gastric cancer has been decreasing in Japan, but it is still the third-leading cause of cancer-related deaths worldwide [1, 2]. Although advances in chemotherapy have improved the survival of patients with unresectable advanced or recurrent gastric cancer dramatically, the prognosis of patients with type 4 gastric cancer remains poor. In fact, the 5-year overall survival (OS) rate of patients with type 4 gastric cancer has been reported to range from 12.5 to 27.6% [3, 4]. Since type 4 gastric cancer involves diffuse infiltration as an oncological property, tumors invade the entire stomach easily. Moreover, patients with type 4 gastric cancer have a high incidence of serosal penetration and peritoneal dissemination [3, 4]. Preventing peritoneal recurrence after curative surgery is a key issue in the clinical management of patients with type 4 gastric cancer [5]. Consequently, identifying the best therapeutic strategies to improve the prognosis of these patients is important.

According to the 2018 Japanese Gastric Cancer Treatment Guidelines, systemic chemotherapy is recommended as the first-line treatment for patients with distant metastasis [6]. Recent studies have also demonstrated the prognostic significance of conversion surgery after chemotherapy for patients with stage IV gastric cancer [7, 8]. Conversely, neoadjuvant chemotherapy (NAC) has been identified as a promising therapeutic strategy in patients with locally advanced gastric cancer, such as macroscopic type 4 tumors, large type 3 tumors, bulky lymph node metastasis, and clinical stage III cancer [9, 10]. However, the indications for and prognostic significance of conversion surgery or NAC remain uncertain

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for patients with type 4 gastric cancer. We conducted this study to examine tumor response and surgical findings after chemotherapy in patients with type 4 gastric cancer and to assess the relationship between clinicopathological findings and whether surgery is performed. The indications for and prognostic impact of surgery after chemotherapy were also investigated in responders.

Methods

Patients

The subjects of this retrospective study were 67 patients (30 men and 37 women; age range, 30–87 years; mean age, 62.5 years) with type 4 gastric cancer, who underwent chemotherapy at Kagoshima University Hospital (Kagoshima, Japan) between February 2002 and November 2019. Patients with synchronous or metachronous cancer in other organs were excluded from the analysis. The data analyzed were blood examination results, as well as esophagogastroduodenoscopy, endoscopic ultrasonography, and computed tomography findings before chemotherapy. Furthermore, 40 patients without peritoneal dissemination identified by radiological examinations underwent staging laparoscopy before starting chemotherapy. Patients were classified and staged based on the TNM classification for gastric carcinoma [11].

We used the "opt-out" method as a way to obtain informed consent from patients. The Ethics Committee of Kagoshima University approved this retrospective study (approval number: 200015).

Evaluation of tumor response

Tumor response was assessed after every three cycles of chemotherapy and categorized according to the Response Evaluation Criteria in Solid Tumors (RECIST) as progressive disease (PD) or non-PD in the present study [12]. Survival time was defined as from the date of chemotherapeutic initiation to the date of death or last follow-up.

Clinical indication for surgery

Surgery after chemotherapy was indicated for patients with a performance status (PS) of 0–2, those with non-PD, those with tumors predicted able to be curatively resected, those with satisfactory physical condition, and at the physician's discretion. These patients underwent staging laparotomy or laparoscopy before gastrectomy. When patients had noncurative factors during staging laparotomy or laparoscopy, curative gastrectomy was postponed, and further chemotherapy was given.

Evaluation of residual tumor and histological response

Residual tumor status postoperatively and the histological response of primary tumors were based on the Japanese classification of gastric carcinoma [13]. The surgical status was grouped into R0, R1, and R2 according to the presence or absence of residual tumors. Histological response was classified into grades 0, 1a, 1b, 2, and 3.

Statistical analysis

The relationship between surgery and clinicopathological factors was assessed using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. Kaplan–Meier survival curves were generated and prognostic differences were evaluated by the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox proportional hazards regression modeling). All data were analyzed using JMP14 (SAS Institute Inc., Cary, NC, USA). A p value of < 0.05 was considered significant.

Results

Clinicopathological factors

Table 1 summarizes the clinicopathological factors of the 67 patients. Five (7.5%) patients had clinical T3 tumors and 62 (92.5%) had T4 tumors. With regard to lymph node metastasis, 23 (34.3%), 12 (17.9%), 17 (25.4%), and 15 (22.4%) patients had the clinical nodal status of N0, N1, N2, and N3, respectively. Fifty-eight patients had distant metastasis, with at least peritoneal dissemination in 55 patients (82.1%). Seven patients (10.4%) had more than two distant metastatic sites, with liver metastasis, distant lymph node metastasis, ovarian metastasis, and metastasis of the small intestine, identified in five, five, one, and one, respectively.

Among the 67 patients enrolled in this study, 33 (49.3%) received platinum-based chemotherapy and 34 (50.7%) received taxane-based chemotherapy as the first-line regimen. Platinum-based regimens included S-1 plus cisplatin ($n = 7$), capecitabine plus cisplatin ($n = 10$), S-1 plus oxaliplatin ($n = 14$), and capecitabine plus oxaliplatin ($n = 2$). Eight patients with positive human epidermal growth factor receptor 2 expression received trastuzumab combined with platinum-based chemotherapy. In contrast, taxane-based regimens included S-1 plus intravenous paclitaxel ($n = 16$), S-1 plus intraperitoneal and intravenous paclitaxel ($n = 14$), S-1 plus nab-paclitaxel ($n = 1$),

Table 1 Clinicopathological factors ($n=67$)

Factor	*n* (%)
Gender	
Male	30 (44.8)
Female	37 (55.2)
Mean age (range), years	62.5 (30–87)
First-line chemotherapeutic regimen	
Platinum-based	33 (49.3)
Taxane-based	34 (50.7)
Tumor location	
Whole	29 (43.3)
Upper	18 (26.9)
Middle	11 (16.4)
Lower	9 (13.4)
Depth of tumor invasion	
cT3	5 (7.5)
cT4	62 (92.5)
Lymph-node metastasis	
cN0	23 (34.3)
cN1	12 (17.9)
cN2	17 (25.4)
cN3	15 (22.4)
Clinical stage	
II	5 (7.5)
III	4 (6.0)
IV	58 (86.6)
Number of distant metastatic sites	
0	9 (13.4)
1	51 (76.1)
2–4	7 (10.4)
Peritoneal dissemination	
P0	12 (17.9)
P1	55 (82.1)
Histological type	
Differentiated	3 (4.5)
Undifferentiated	64 (95.5)

and S-1 plus docetaxel ($n=3$). The median number of first-line chemotherapy cycles was three (range, 1–32).

Tumor response and survival after chemotherapy

Based on the tumor response to chemotherapy, being PD in 16 patients and non-PD in 51 patients, the disease control rate was 76.1% (51/67). The median survival times of the patients with PD and those with non-PD were 159 days and 757 days, respectively (Fig. 1). The survival difference based on tumor response was significant ($p<0.0001$).

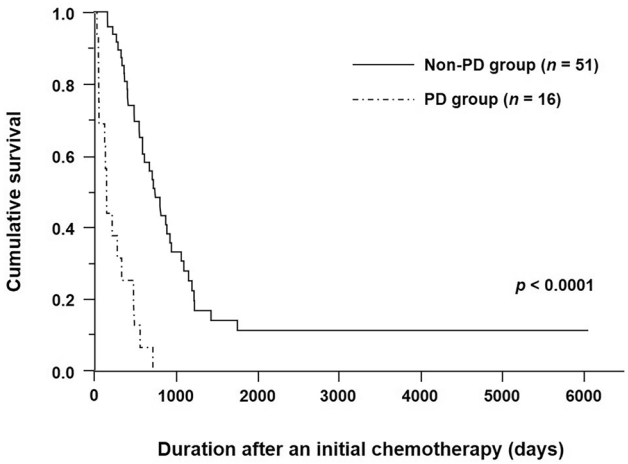

Fig. 1 Kaplan–Meier survival curves based on tumor response

Surgery after chemotherapy and pathological findings

A total of 23 patients (34.3%) underwent surgery after chemotherapy. Laparotomy or laparoscopy was performed before gastrectomy and the absence of peritoneal dissemination was confirmed in all patients. Surgery was performed after first-line chemotherapy in 22 patients and after second-line chemotherapy in 1 patient. Table 2 summarizes the surgical procedures and pathological findings. Twenty-two (95.7%) patients underwent total gastrectomy and one (4.3%) underwent proximal gastrectomy. Moreover, D1, D1+, and D2 lymphadenectomy was performed in 2 (8.7%), 6 (26.1%), and 15 (65.2%) patients, respectively. D1 or D1+lymphadenectomy was also performed in seven patients: for proximal gastrectomy ($n=1$), because of the advanced age of 87 years ($n=1$), for severe co-morbidities ($n=2$), and because of malnutrition plus a PS of 1–2 ($n=4$). As two (8.7%) patients had no viable tumor cells in the primary site, the depth of tumor invasion was staged as T0; however, 1 (4.3%), 5 (21.7%), and 15 (65.2%) patients had pathological stage T2, T3, and T4 tumors, respectively; and 9 (39.1%), 2 (8.7%), and 12 (52.2%) patients had pathological N0, N1, and N3, respectively. R0, R1, and R2 resection was performed in 21 (91.3%), 1 (4.3%), and 1 (4.3%) patient, respectively. Histological response of grade 1a, 1b, 2, and 3 was confirmed in 18 (78.3%), 1 (4.3%), 2 (8.7%), and 2 (8.7%) patients, respectively.

Relationship between clinicopathological factors and whether surgery was performed

The mean age (±standard deviation) of the patients who underwent surgery (surgery group; $n=23$) and those who did not (no surgery group; $n=44$) was 58.0±13.7 and

Table 2 Surgical procedures and pathological findings (n = 23)

Factor	*n* (%)
Surgical procedure	
Total gastrectomy	22 (95.7)
Proximal gastrectomy	1 (4.3)
Lymph-node dissection	
D1	2 (8.7)
D1 +	6 (26.1)
D2	15 (65.2)
Depth of tumor invasion	
pT0 (no viable tumor cells)	2 (8.7)
pT1	0 (0.0)
pT2	1 (4.3)
pT3	5 (21.7)
pT4	15 (65.2)
Lymph node metastasis	
pN0	9 (39.1)
pN1	2 (8.7)
pN2	0 (0.0)
pN3	12 (52.2)
Residual tumor status	
R0	21 (91.3)
R1	1 (4.3)
R2	1 (4.3)
Histological response	
Grade 1a	18 (78.3)
Grade 1b	1 (4.3)
Grade 2	2 (8.7)
Grade 3	2 (8.7)

64.9 ± 12.6 years, respectively (Table 3). Consequently, surgery was significantly correlated with age ($p = 0.0412$). Moreover, surgery was significantly associated with the first-line chemotherapeutic regimen, lymph node metastasis, clinical stage, number of distant metastatic sites, and peritoneal dissemination ($p = 0.0096$, $p = 0.0024$, $p = 0.0059$, $p = 0.0128$, and $p = 0.0020$, respectively; Table 3). A non-PD tumor response was noted in 22 (95.7%) of the 23 patients in the surgery group, whereas a PD response was noted in 15 (34.1%) of the 44 patients in the no-surgery group. Accordingly, tumor response was significantly associated with whether or not surgery was performed ($p = 0.0066$; Table 3).

Survival assessment in the surgery and no-surgery groups

The 3-year OS rate in the surgery and no-surgery groups was 56.4% and 6.2%, respectively ($p < 0.0001$; Fig. 2). Univariate analysis identified that age, first-line chemotherapeutic regimen, lymph node metastasis (cN0-1 vs. cN2-3), tumor response, and surgery were significantly associated with survival between the surgery and no-surgery groups ($p = 0.0394$, $p = 0.0311$, $p = 0.0006$, $p < 0.0001$, and $p < 0.0001$, respectively; Table 4). Multivariate analysis selected tumor response and surgery as independent prognostic factors ($p = 0.0001$ and $p = 0.0009$, respectively; Table 4).

Univariate and multivariate analyses in the surgery group alone

Univariate analysis identified that lymph node metastasis (pN0-1 vs. pN2-3) and residual tumor status (R0 vs. R1-2) were significantly correlated with survival in the surgery group ($p = 0.0121$ and $p = 0.0096$, respectively; Table 5). Similarly, multivariate analysis identified lymph node metastasis and residual tumor status as independent prognostic factors ($p = 0.0258$ and $p = 0.0458$, respectively; Table 5).

Discussion

It is well documented that the prognosis of patients with type 4 gastric cancer is generally much poorer than that of those with other macroscopic types of gastric cancer [3, 4]. Currently, patients with type 4 gastric cancer are treated with surgery and/or chemotherapy, while a novel therapeutic strategy is being actively sought for further prognostic improvement. However, few investigators have assessed the clinical indications for, and prognostic impact of, NAC and surgical interventions in these patients. Thus, we conducted this study to analyze the clinicopathological factors, tumor response to chemotherapy, presence or absence of surgery, and survival of patients with type 4 gastric cancer who underwent chemotherapy, and investigate the indications for and prognostic importance of surgery after chemotherapy.

Type 4 gastric cancer manifests aggressive tumor behavior. The incidence of lymph node metastasis has been reported to range from 79.5 to 94.0% [5, 14, 15]. In the present series, it was 60.9%, even in patients who received chemotherapy, demonstrating the lymphatic spread of tumor cells in these patients. Patients with type 4 gastric cancer also have a high incidence of peritoneal dissemination, including positive peritoneal cytology. A meta-analysis demonstrated that the odds ratio for peritoneal dissemination was 3.91 in patients with type 4 gastric cancer, compared with other macroscopic types of gastric cancer [16]. Surprisingly, our study identified a positive peritoneal dissemination rate of 82.1% (55/67) and most patients underwent staging laparoscopy. However, the false-negative rate of staging laparoscopy for detecting peritoneal dissemination is reported to be 0–17.2% [17]. Accordingly, these findings suggest that staging laparoscopy plays an important role in the accurate assessment of peritoneal dissemination in patients with type

Table 3 Correlation between clinicopathological factors and whether surgery was performed or not

Factor	Treatments, *n* (%)		*p* value
	Surgery group (*n* = 23)	No-surgery group (*n* = 44)	
Gender			0.0724
Male	14 (60.9)	16 (36.4)	
Female	9 (39.1)	28 (63.6)	
Mean age, years	58.0 ± 13.7	64.9 ± 12.6	0.0412
First-line chemotherapeutic regimen			0.0096
Platinum-based	6 (26.1)	27 (61.4)	
Taxane-based	17 (73.9)	17 (38.6)	
Cycle number of the first -line chemotherapy	6.7	5.4	0.0875
Tumor location			0.7804
Whole/upper	17 (73.9)	30 (68.2)	
Middle/lower	6 (26.1)	14 (31.8)	
Depth of tumor invasion			1.0000
cT3	2 (8.7)	3 (6.8)	
cT4	21 (91.3)	41 (93.2)	
Lymph-node metastasis			0.0024
cN0–1	18 (78.3)	17 (38.6)	
cN2–3	5 (21.7)	27 (61.4)	
Clinical stage			0.0059
II–III	7 (30.4)	2 (4.5)	
IV	16 (69.6)	42 (95.5)	
Number of distant metastatic sites			0.0128
0	7 (30.4)	2 (4.5)	
1	14 (60.9)	37 (84.1)	
2–4	2 (8.7)	5 (11.4)	
Peritoneal dissemination			0.0020
P0	9 (39.1)	3 (6.8)	
P1	14 (60.9)	41 (93.2)	
Histological type			1.0000
Differentiated	1 (4.3)	2 (4.5)	
Undifferentiated	22 (95.7)	42 (95.5)	
Tumor response to chemotherapy			0.0066
PD	1 (4.3)	15 (34.1)	
non-PD	22 (95.7)	29 (65.9)	

PD progressive disease

4 gastric cancer. Staging laparoscopy is needed to establish a therapeutic plan for these patients without peritoneal dissemination identified by radiological examinations.

Interestingly, Kim et al. [5] reported that multivariate analysis revealed surgical curability was not a significant prognostic predictor for patients with type 4 gastric cancer ($p = 0.187$). They concluded that the role of surgery alone was limited in improving the prognosis of patients with type 4 gastric cancer [5]. Recently, chemotherapy has also been given as initial treatment, in line with the dramatic advances in chemotherapy and the potential utility of NAC for all patients with type 4 gastric cancer. The present study indicated a high disease control rate to chemotherapy, of 76.1%. Furthermore, the prognosis of patients with non-PD was significantly better than that of those with PD and multivariate analysis showed tumor response as an independent prognostic factor. In surgical specimens, the pathological response rate of grade ≥ 1b was 21.7% (5/23). A phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for patients with clinically resectable type 4 and large type 3 gastric cancers showed a pathological response rate of 46.9% (23/49) [18]. Consequently, these findings support that chemotherapy is a promising tool to control tumor progression during the initial therapeutic strategy.

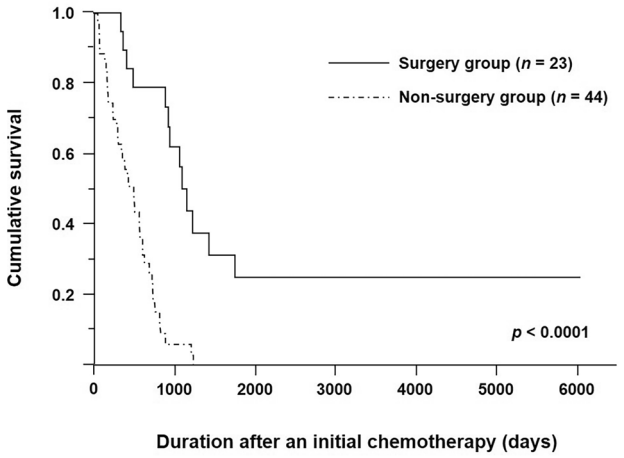

Fig. 2 Kaplan–Meier survival curves based on whether surgery was performed or not

The present study found that the pathological response rate of grade 3 was only 8.7% (2/23). Similarly, Iwasaki et al. [18] reported that 2.0% (1/49) of patients with clinically resectable type 4 and large type 3 gastric cancer had a pathological response of grade 3. Moreover, the prognosis of our surgery group was significantly more favorable than that of our no-surgery group. Unfortunately, the 5-year OS rate of the no-surgery group was 0% (Fig. 2). As tumor cells cannot be eliminated with chemotherapy alone, additional surgery to remove residual tumors may contribute to improving the prognosis of responders.

The incidence of patients with non-PD in our surgery group was 95.7% (22/23). Although this indicates a close relationship between tumor response and surgery, the most suitable indication for surgery after chemotherapy for responders with type 4 gastric cancer remains unclear. Recent studies have identified several important predictors of prognosis based on univariate and multivariate analyses in patients with type 4 gastric cancer [4, 14]. An et al. [4] reported that the hazard ratios of the residual tumor status (R0 vs. R1) and nodal status (N0 vs. N2) were 2.145 ($p < 0.001$) and 2.504 ($p < 0.001$), respectively. In the present study, multivariate analysis revealed that lymph node metastasis and residual tumor status alone were independent predictors for OS in our surgery group. Accordingly, these findings may suggest that lymph node metastasis and residual tumor status are the most important factors determining the clinical indication for the surgical strategy in patients with type 4 gastric cancer. The R0 resection rate was 91.3% (21/23) in this study, which shows high surgical curability in patients with type 4 gastric cancer with aggressive malignant behavior. Furthermore, preoperative chemotherapy might enhance the surgical curability of the clinical management of patients with type 4 gastric cancer.

The present study had several limitations because it was a retrospective analysis of a small number of patients ($n = 67$) in a single institution. Furthermore, the chemotherapeutic regimen, its duration, and the clinical indications of surgery were based on the patients' condition, the registration of clinical trials, or the physician's discretion. These limitations may have resulted in bias that influenced several results, including the univariate and multivariate analyses. Consequently, larger prospective multicenter studies with longer follow-up periods are required to strengthen our conclusions. Moreover, we focused on patients who received chemotherapy as initial treatment in this study; however, five patients with type 4 gastric cancer underwent upfront surgery during this study period at our hospital. The 3-year and 5-year OS rates of these five patients were 25.0% and 0%, respectively (data not shown). These patients had a poor prognosis, although further study is needed to investigate the clinical significance of upfront surgery.

In conclusion, the findings of this study suggest that surgery after chemotherapy for type 4 gastric cancer may contribute to improving the prognosis of responders with N0-1 status who undergo curative R0 resection.

Table 4 Univariate and multivariate analyses of survival of all the patients ($n=67$)

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Gender			0.1768			
Female	1.000	Reference				
Male	0.679	0.387–1.191				
Age (years)			0.0394			0.1814
< 70	1.000	Reference		1.000	Reference	
≥ 70	1.832	1.030–3.258		1.500	0.828–2.719	
First-line chemotherapeutic regimen			0.0311			0.7941
Platinum-based	1.000	Reference		1.000	Reference	
Taxane-based	0.529	0.296–0.944		1.086	0.586–2.013	
Tumor location			0.2102			
Whole/upper	1.000	Reference				
Middle/lower	1.453	0.810–2.605				
Depth of tumor invasion			0.3233			
cT3	1.000	Reference				
cT4	1.803	0.560–5.803				
Lymph-node metastasis			0.0006			0.5769
cN0–1	1.000	Reference		1.000	Reference	
cN2–3	2.728	1.543–4.823		1.207	0.623–2.340	
Peritoneal dissemination			0.1301			
P0	1.000	Reference				
P1	1.933	0.823–4.539				
Histological type			0.8089			
Differentiated	1.000	Reference				
Undifferentiated	0.865	0.266–2.807				
Tumor response to chemotherapy			< 0.0001			0.0001
non-PD	1.000	Reference		1.000	Reference	
PD	6.604	3.360–12.982		4.123	1.990–8.540	
Surgery			< 0.0001			0.0009
Absence	1.000	Reference		1.000	Reference	
Presence	0.178	0.084–0375		0.229	0.096–0.547	

CI confidence interval, *PD* progressive disease

Table 5 Univariate and multivariate analyses of survival in the surgery group ($n=23$)

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Gender			0.2919			
Female	1.000	Reference				
Male	0.551	0.182–1.669				
Age (years)			0.4174			
< 70	1.000	Reference				
≥ 70	1.715	0.466–6.310				
First-line regimen of chemotherapy			0.2868			
Platinum-based	1.000	Reference				
Taxane-based	0.405	0.077–2.135				
Tumor location			0.0733			
Whole/upper	1.000	Reference				
Middle/lower	3.567	0.887–14.346				
Tumor size (mm)			0.9096			
< 100	1.000	Reference				
≥ 100	0.932	0.279–3.118				
Depth of tumor invasion			0.1734			
pT0–3	1.000	Reference				
pT4	2.482	0.671–9.187				
Lymph-node metastasis			0.0121			0.0258
pN0–1	1.000	Reference		1.000	Reference	
pN2–3	5.517	1.452–20.959		4.786	1.209–18.954	
Residual tumor status			0.0096			0.0458
R0	1.000	Reference		1.000	Reference	
R1–2	13.672	1.891–98.872		7.655	1.039–56.423	

CI confidence interval

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Declarations

Conflict of interest We have no competing interests to declare.

Ethics approval This study was approved by the Ethics Committee of Kagoshima University (approval number: 200015).

Informed consent We conducted a retrospective study and used the "opt-out" method as a way to obtain informed consent from patients.

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