



Original article

Gastric cancer with extragastric lymph node metastasis: multivariate prognostic study

NORIO SHIRAIISHI¹, YOSUKE ADACHI¹, SEIGO KITANO¹, TOSHIO BANDO¹, MASAFUMI INOMATA¹, KAZUHIRO YASUDA¹, JUNKO TSUCHIHASHI², and NAOKO KINUKAWA²

¹First Department of Surgery, Oita Medical University, 1-1 Idaigaoka, Hasama-machi, Oita 879-5593, Japan

²Department of Medical Informatics, Kyushu University, Fukuoka, Japan

Abstract

Background. Although many authors have investigated the prognostic factors of gastric cancer, there are few comprehensive studies on the prognosis of patients with extensive lymph node metastasis. The aim of this study was to clarify the prognostic factors of gastric cancer with extragastric lymph node metastasis, using multivariate analysis.

Methods. The study population consisted of 121 patients who had undergone radical gastrectomy and extended lymph node dissection (D2, D3) for gastric cancer with extragastric lymph node metastasis. We examined 18 clinicopathologic factors, including the type of gastrectomy, tumor size, depth of wall invasion, status of lymph node metastasis, and stage of disease. Survival rates were analyzed by the Kaplan-Meier and Mantel-Cox methods, and multivariate analysis was done using the Cox proportional hazards model.

Results. The overall 5-year survival rate was 32%, and the 5-year survival rate after curative gastrectomy was 37%. Overall survival rate was associated with the type of gastrectomy, stage of disease, operative curability, tumor size, depth of wall invasion, and anatomical distribution of positive nodes, whereas the survival rate after curative gastrectomy was correlated with the type of gastrectomy, stage of disease, tumor size, gross type, and depth of wall invasion. Independent prognostic factors were operative curability and depth of wall invasion, and survival after curative gastrectomy was influenced only by the depth of wall invasion (mucosa and submucosa [T1], muscularis and subserosa [T2] vs serosa [T3]).

Conclusion. In patients with gastric cancer with extragastric lymph node metastasis, independent prognostic factors after gastrectomy were operative curability and depth of wall invasion. Long-term survival can be achieved when the patients have no serosal invasion (T1, T2) and are treated by curative gastrectomy.

Key words Stomach · Cancer · Gastric cancer · Lymph node metastasis · Prognosis · Survival

Introduction

Depth of wall invasion and status of lymph node metastasis are the most important factors for estimating outcome after gastrectomy for cancer [1,2]. The prognosis of patients with superficial gastric cancer and node-negative gastric cancer is excellent [3,4], whereas the survival rate for patients with serosal invasion and lymph node metastasis is not good [5,6]. In patients with gastric cancer associated with extragastric lymph node metastasis, many patients die of recurrence soon after gastrectomy, but some are alive without recurrence for more than 10 years [7,8].

Although many authors have investigated the prognostic factors of gastric cancer [1–8,9], there are few comprehensive studies of the surgical results and prognostic factors in patients with gastric cancer with extragastric lymph node metastasis. In the present study, we investigated prognostic factors in patients with gastric cancer in whom lymph node metastasis was not confined to the perigastric lymph nodes, but reached the extragastric lymph nodes. The clinicopathologic factors influencing the survival after gastrectomy were examined based on survival curves, and the prognostic factors of gastric cancer involving the extragastric lymph nodes were clarified using multivariate analysis.

Patients and methods

Our study population consisted of 121 patients who had undergone radical gastrectomy and extended lymph node dissection (D2, D3) at the First Department of Surgery, Oita Medical University, between June 1982 and October 1998. All patients had histologically confirmed primary adenocarcinoma of the stomach involving extragastric lymph node metastasis (n2, n3). Excluded were patients with tumors invading the

adjacent organs, those with liver metastasis, and those with peritoneal dissemination.

Clinicopathologic findings obtained from operation records and pathology reports were the age and sex of the patients; type of gastrectomy; extent of lymph node dissection; location, size, gross type, and histologic type of tumors; depth of wall invasion; presence of lymphatic and vascular invasions; status of lymph node metastasis; stage of disease; and operative curability. These parameters were determined according to the Japanese classification of gastric carcinoma outlined by the Japanese Gastric Cancer Association [10].

Histologic type was classified into two major categories: well differentiated (including papillary and tubular adenocarcinomas, poorly differentiated medullary carcinoma, and mucinous carcinoma of well differentiated type) and poorly differentiated (including poorly differentiated adenocarcinoma of common type, signet-ring cell carcinoma, and mucinous carcinoma of poorly differentiated type) [11]. Lymphatic and vascular invasions were regarded as negative when the findings were absent or slight (ly0, ly1; v0, v1) and positive when the findings were moderate or marked (ly2, ly3; v2, v3). Operation was regarded as curative when no residual cancer cells were considered to have been left behind.

Status of lymph node metastasis was classified according to the anatomical distribution of positive lymph nodes outlined by the Japanese Gastric Cancer Association (n2, n3) [10], total number of positive lymph nodes determined by the International Union Against Cancer (UICC) classification (N1, 1–6; N2, 7–15; N3, ≥ 16) [12], and level of positive lymph nodes was determined irrespective of tumor location (level II, level III) [13]. Whether extragastric lymph node metastasis was confined to the lymph nodes along the left gastric artery (station no. 7) or to the lymph nodes along the common hepatic artery (station no. 8) was also checked.

The outcome of all patients was examined through a follow-up study, including outpatient visits, telephone contact, and examination of death certificates. The follow-up period for the survivors ranged from 12 to 150 months, with a mean of 67 months and a median of 61 months; only patients who died of gastric cancer were regarded as cases of tumor-related death. Seventy-two patients died of recurrence; in 48 of these patients the pattern of recurrence was identified (local and/or peritoneal recurrence in 34, liver metastasis in 6, bone metastasis in 3, lung metastasis in 2, lymph node metastasis in 2, and esophageal recurrence in 1). The remaining 24 patients died of recurrent gastric cancer, but the pattern of recurrence was not identified. Cumulative survival rates were calculated by the Kaplan-Meier method, and survival curves were tested by the Mantel-Cox method. Multivariate analysis was performed using the Cox proportional hazards model.

Results

The overall 5-year survival rate was 32%, and the 50% survival period was 19 months (Fig. 1). Survival after gastrectomy was associated with the type of gastrectomy (distal vs total; $P < 0.05$), stage of disease (II, IIIa vs IIIb, IV; $P < 0.01$), operative curability (curative vs noncurative; $P < 0.01$), tumor size (< 10 cm vs ≥ 10 cm; $P < 0.01$), depth of wall invasion (T1, T2 vs T3; $P < 0.01$; within vs beyond muscularis; $P < 0.01$), and anatomical distribution of positive lymph nodes (n2 vs n3; $P < 0.05$) (Table 1). Although the survival was influenced by the number of positive lymph nodes (N1, N2 vs N3), the difference was not significant ($P = 0.051$). The 5-year survival rates for patients with 1–2 positive nodes (25%), 3–5 positive nodes (48%), 6–15 positive nodes (36%), and ≥ 16 positive nodes (18%) were not significantly different.

In patients with curative gastrectomy, the 5-year survival rate was 37%, and the 50% survival period was 26 months. Table 2 shows that the survival after curative gastrectomy was associated with the type of gastrectomy (distal vs total; $P < 0.01$), stage of disease (II, IIIa vs IIIb, IV; $P < 0.01$), tumor size (< 10 cm vs ≥ 10 cm; $P < 0.01$), gross type (localized vs infiltrative; $P < 0.05$), and depth of wall invasion (T1, T2 vs T3; $P < 0.01$; within vs beyond muscularis; $P < 0.01$). Although the

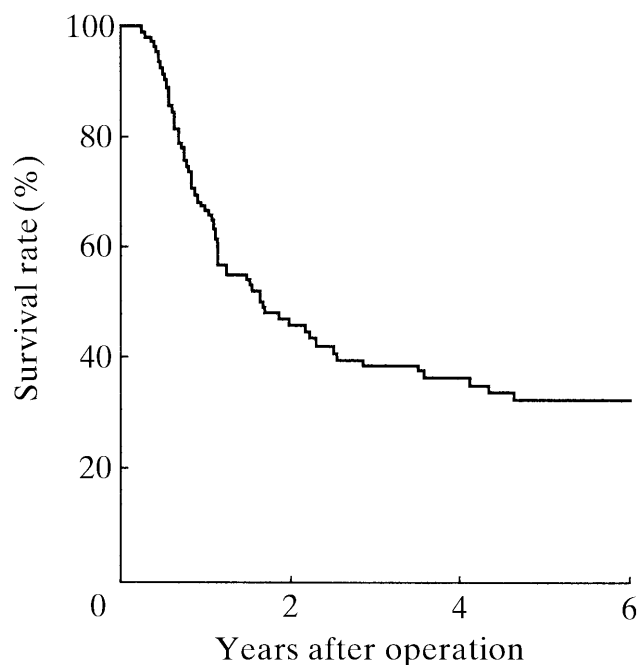


Fig. 1. Survival curve of patients who underwent gastrectomy for gastric cancer with extragastric lymph node metastasis. The overall 5-year survival rate was 32%, and the 50% survival period was 19 months

Table 1. Survival after gastrectomy

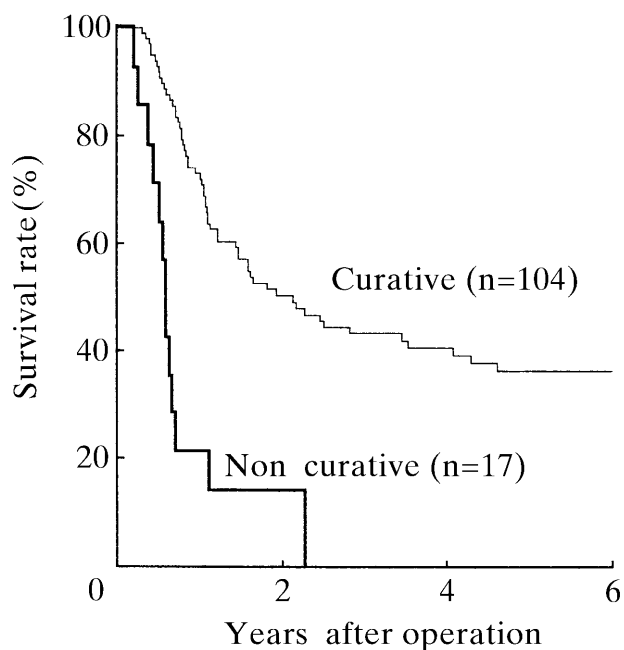
Variables	Number of patients	5-Year survival rate (%)	50% Survival period (months)	<i>P</i> value
Age (years)				
<60	41	37.3	22.1	
≥60	80	29.6	19.3	NS
Sex				
Male	77	28.4	18.0	
Female	44	39.3	30.3	NS
Gastrectomy				
Distal	59	48.9	41.7	
Total	62	18.5	17.5	<0.05
Dissection				
D2	53	31.4	20.0	
D3	68	31.4	17.7	NS
Stage				
II, IIIa	34	62.4	NC	
IIIb, IV	87	19.5	14.8	<0.01
Curability				
Curative	104	36.6	25.8	
Noncurative	17	0.0	7.0	<0.01
Location				
Lower two-thirds	93	37.7	23.4	
Upper one-third	28	14.2	18.0	NS
Size (cm)				
<10	86	42.2	29.9	
≥10	35	10.4	14.7	<0.01
Gross type				
Localized	32	49.5	19.3	
Infiltrative	89	25.7	19.5	NS
Histologic type				
Well differentiated	36	44.5	27.4	
Poorly differentiated	85	27.2	17.7	NS
Depth of invasion (1)				
T1, T2	50	54.0	NC	
T3	71	16.7	14.7	<0.01
Depth of invasion (2)				
Within muscularis	22	64.2	NC	
Beyond muscularis	99	25.2	14.7	<0.01
Lymphatic invasion				
Absent	35	39.5	19.4	
Present	86	29.8	19.5	NS
Vascular invasion				
Absent	111	34.6	19.5	
Present	10	0.0	13.2	NS
Anatomical distribution of positive nodes (Japanese classification)				
n2	80	39.4	27.4	
n3	41	17.1	13.3	<0.05
Number of positive nodes (TNM classification)				
N1, N2 (≤15)	80	39.4	25.8	
N3 (≥16)	41	18.6	17.5	0.051
Level of positive nodes				
Level II	61	39.6	30.3	
Level III	60	24.2	17.7	NS
Positive extragastric nodes				
Station no. 7 only	20	45.4	55.4	
Others	101	30.0	17.5	NS
Positive extragastric nodes				
Station no. 8 only	15	32.7	12.6	
Others	106	31.8	19.4	NS

NS, Not significant; T1, mucosa and submucosa; T2, muscularis and subserosa; T3, serosa; station no. 7, lymph nodes along left gastric artery; station no. 8, lymph nodes along common hepatic artery; NC, not calculated

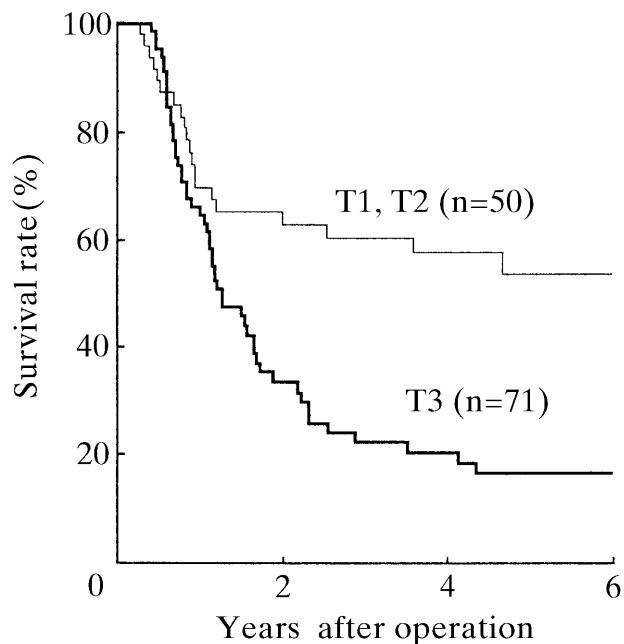
Table 2. Survival after curative gastrectomy

Variables	Number of patients	5-Year survival rate (%)	50% Survival period (months)	<i>P</i> value
Age (years)				
<60	36	42.7	34.0	
≥60	68	33.2	19.5	NS
Sex				
Male	67	31.2	19.4	
Female	37	46.8	55.4	0.054
Gastrectomy				
Distal	51	56.3	NC	
Total	53	20.4	18.0	<0.01
Dissection				
D2	42	37.4	49.1	
D3	62	35.0	19.3	NS
Stage				
II, IIIa	33	64.3	NC	
IIIb, IV	71	22.9	19.3	<0.01
Location				
Lower two-thirds	80	43.3	41.7	
Upper one-third	24	14.9	18.0	0.052
Size (cm)				
<10	75	47.3	42.6	
≥10	29	11.9	17.5	<0.01
Gross type				
Localized	26	59.4	NC	
Infiltrative	71	28.4	22.1	<0.05
Histologic type				
Well differentiated	33	47.3	29.9	
Poorly differentiated	85	31.4	19.5	NS
Depth of invasion (1)				
T1, T2	43	62.0	NC	
T3	61	18.6	17.5	<0.01
Depth of invasion (2)				
Within muscularis	20	71.2	NC	
Beyond muscularis	84	28.5	18.0	<0.01
Lymphatic invasion				
Absent	34	40.8	19.4	
Present	70	35.0	25.8	NS
Vascular invasion				
Absent	97	38.5	26.3	
Present	7	0.0	13.2	NS
Anatomical distribution of positive nodes (Japanese classification)				
n2	77	41.1	34.0	
n3	27	23.2	17.7	NS
Number of positive nodes (TNM classification)				
N1, N2 (≤15)	74	42.2	29.9	
N3 (≥16)	30	23.5	19.4	NS
Level of positive nodes				
Level II	57	42.6	34.0	
Level III	47	28.9	20.0	NS
Positive extragastric nodes				
Station no. 7 only	20	45.4	55.4	
Others	84	34.7	22.1	NS
Positive extragastric nodes				
Station no. 8 only	20	36.5	25.8	
Others	84	32.7	12.6	NS

NS, Not significant; T1, mucosa and submucosa; T2, muscularis and subserosa; T3, serosa; station no. 7, lymph nodes along left gastric artery; station no. 8, lymph nodes along common hepatic artery



a



b

Fig. 2a,b. Factors associated with survival after gastrectomy were **a** operative curability and **b** depth of wall invasion. The survival curves show that only curative gastrectomy and serosa-negative tumor brought about a favorable outcome in gastric cancer with extragastric lymph node metastasis. *T1*, mucosa and submucosa; *T2*, muscularis and subserosa; *T3*, serosa

survival was influenced by the location of tumors (lower two-thirds vs upper one-third), the difference was not significant ($P = 0.052$). The anatomical distribution and number and level of positive lymph nodes were not associated with the survival after curative gastrectomy.

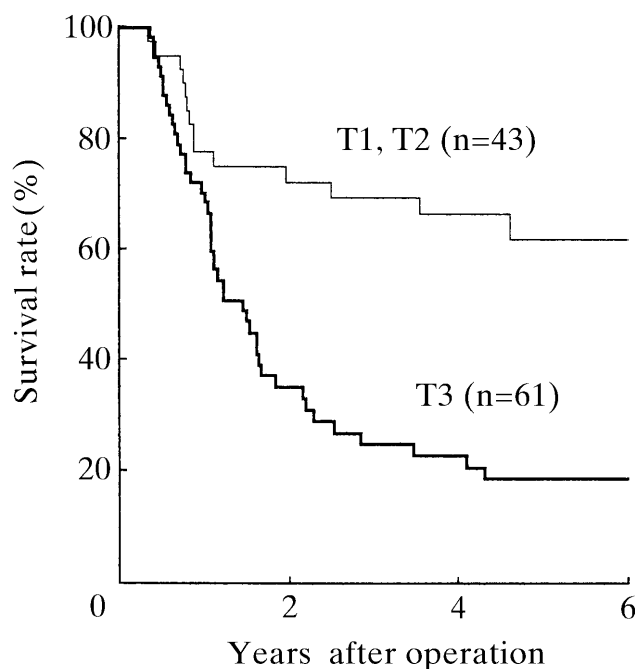


Fig. 3. The factor associated with survival after curative gastrectomy was the depth of wall invasion. The survival curve shows that *T1* or *T2* tumor brought about a favorable outcome in gastric cancer with extragastric lymph node metastasis

Table 3 shows the independent prognostic factors. Analysis based on the 19 factors listed in Table 1 revealed that the factors associated with survival after gastrectomy were operative curability and depth of wall invasion (Fig. 2). However, analysis based on the 18 factors listed in Table 2 revealed that the factor associated with the survival after curative gastrectomy was depth of wall invasion (Fig. 3).

Discussion

The results of the present study indicated that the prognosis of patients with gastric cancer with extragastric lymph node metastasis was independently influenced by operative curability and depth of wall invasion, and, when gastrectomy was curative, prognosis was determined by the depth of wall invasion. Therefore, the only candidates for long-term survival are those patients without serosal invasion (*T1*, *T2*) who are treated by curative radical gastrectomy.

Several authors have emphasized that curative resection is essential for the treatment of patients with gastric cancer, and that curability, based on the operative and pathological findings, is important for evaluating long-term survival after gastrectomy [9]. In patients with extensive lymph node metastasis, however, curative resection can be achieved only by radical gastrectomy and

Table 3. Independent prognostic factors

Variables	Regression coefficient	Standard error	Odds ratio (95% confidence interval)	P value
Based on the 18 factors presented in Table 1 (all gastrectomy cases)				
Curability (curative vs noncurative)	1.39	0.32	4.01 (2.14–7.53)	<0.01
Depth of invasion (T1, T2 vs T3)	0.83	0.27	2.29 (1.35–3.89)	<0.01
Based on the 17 factors presented in Table 2 (only curative cases)				
Depth of invasion (T1, T2 vs T3)	1.21	0.31	3.36 (1.83–6.16)	<0.01

T1, Mucosa and submucosa; T2, muscularis and subserosa; T3, serosa

extended lymph node dissection. The procedures have been advocated by some Japanese gastric surgeons [14,15], although several other groups have emphasized that radical gastrectomy with extended lymph node dissection is associated with high morbidity and mortality [16–18].

The depth of wall invasion is one of the most important prognostic factors in gastric cancer [1,2,6,8]. The present study confirmed that the depth of wall invasion was a useful parameter for predicting the survival of patients with gastric cancer involving extragastric lymph nodes. Some authors have clarified that not only the presence or absence of serosal invasion but also the width of serosal invasion is linked to survival after gastrectomy [5]. In our series, serosal invasion was absent in 50 (41%) of the 121 patients and in 43 (41%) of the 104 patients with curative gastrectomy. Thus, approximately 40% of patients with extragastric lymph node metastasis are candidates for survivors.

In the present study, the 5-year survival rate after distal gastrectomy was significantly higher than that after total gastrectomy. This confusing finding was considered to have resulted from the fact that more tumors located in the upper one-third of the stomach and more tumors larger than 10cm in size had been treated by total gastrectomy. Previous reports on a randomized clinical trial show that subtotal gastrectomy is equivalent to total gastrectomy in terms of 5-year survival, but is superior to total gastrectomy in terms of the patients' nutritional state and quality of life [19,20].

The level and number of lymph node metastases is another important prognostic indicator of gastric cancer [7–10,21]. Table 4 lists the 5-year survival rates of patients with gastric cancer with extragastric lymph node metastasis and shows that the level of lymph node metastasis is associated with survival [22–31]. The 5-year survival rates of n2 and n3 cases in our series were in accordance with those in the literature, and the 5-year survival rate was significantly different between the n2 and n3 cases in most series, including ours (39% vs 17%; $P < 0.05$). In patients with curative gastrectomy, how-

ever, the 5-year survival rate of n3 cases was as high as that of n2 cases. The 5-year survival rate for patients in whom extragastric lymph node metastasis was confined to the nodes along the left gastric artery (station no. 7; 45%, $n = 20$) or to the lymph nodes along the common hepatic artery (station no. 8; 33%, $n = 15$) was not significantly different from that in patients with positive lymph nodes classified as "others" (30%; 32%) (Table 1).

The aim of this study was to clarify the surgical results in patients with gastric cancer with extragastric lymph node metastasis. Therefore, we reviewed the English-language literature in which the survival rate of patients with extragastric lymph node metastasis was examined (n2 and n3 in the Japanese classification). Because recent Western studies, such as those by Roder [32], Manzoni [33], and Karpeh [34], depend on the old TNM classification (N1, within 3cm of the primary tumor; N2, 3cm beyond the primary tumor), whether lymph node metastasis is perigastric or extragastric cannot be determined in these studies. Accordingly, because of this difference in lymph node classification, we have included only reports from Japan, Korea, and Taipei in our literature survey (Table 4).

Whether extended lymph node dissection improves the survival of patients with gastric cancer is still controversial [35–37]. We cannot comment on this problem in regard to our study, because our prognostic analysis was retrospective and historical, and operative strategy and the stage-migration phenomenon are also problems that need to be addressed in assessments of the utility of radical lymph node dissection [38,39]. A prospective, randomized clinical trial should be able to clarify whether D3 gastrectomy is superior to D2 gastrectomy in patients with extragastric lymph node metastasis.

In conclusion, the operative curability and depth of wall invasion were found to be the most significant factors independently associated with survival time after operation for gastric cancer with extragastric lymph node metastasis. Patients with noncurative gastrectomy or those with serosal invasion frequently died of recur-

Table 4. Five-year survival rates of gastric cancer with extragastric lymph node metastasis: review of the literature

Author	Year	n0	n1	n2	n3	P value
Maruyama [22]	1987	85% (1631)	61% (511)	31% (719)	10% (165)	NA
Makino [23]	1991	89% (407)	68% (124)	49% (104)	31% (18)	<0.01*
Isozaki [24]	1993	86% (431)	60% (182)	33% (97)	17% (44)	<0.01**
Wu [25]	1996	91% (223)	54% (104)	39% (115)	22% (40)	<0.01
Yu [26]	1997	86% (436)	45% (236)	29% (116)	19% (98)	<0.01
Kodera [27]	1998	95% (880)	75% (243)	45% (192)	30% (58)	<0.01
Fujii [28]	1999	89% (879)	63% (261)	46% (194)	20% (70)	<0.01**
Ichikura [29]	1999	90% (298)	71% (151)	38% (119)	5% (19)	<0.05
Kato [30]	1999	85% (71)	70% (50)	42% (56)	13% (9)	<0.01
Hayashi [31]	2000	85% (488)	38% (176)	24% (201)	13% (75)	<0.01
Total						
Range		85–95%	38%–75%	24%–49%	5%–31%	
Median		87.5%	62%	38.5%	18%	

*Not significant between n2 and n3 cases; ** $P < 0.05$ between n2 and n3 cases
Numbers in parentheses indicate numbers of patients; NA, not available

rence even after radical gastrectomy and extended lymph node dissection (D2, D3).

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