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Original article

Trends in characteristics of surgically treated early gastric cancer patients after the introduction of gastric cancer treatment guidelines in Japan

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Abstract

Background. The gastric cancer treatment guidelines (Guidelines) of the Japanese Gastric Cancer Association allow endoscopic treatment and a modified gastrectomy for the treatment of early gastric cancer (EGC). Endoscopic treatment is indicated for EGC with a minimal chance of nodal metastasis. Consequently, surgeons will likely treat an increasing number of EGC patients with greater chance of nodal metastasis using a reduced extent of lymphadenectomy. The aim of this study was to investigate the trends in characteristics and long-term oncological outcomes of surgically treated EGC patients after the introduction of the Guidelines.

Methods. Between 2001 and 2003, 696 patients underwent a gastrectomy according to the Guidelines. These 696 patients (the Guidelines group) were retrospectively compared with 635 patients (the control group) who had undergone a gastrectomy between 1991 and 1995 (before the introduction of the Guidelines).

Results. The incidence of nodal metastasis in mucosal cancers was higher in the Guidelines group than in the control group (6.5% vs 2.6%). The proportion of D2 or greater extended lymphadenectomy in the Guidelines group was lower than that in the control group (29.7% vs 62.5%). Nevertheless, the 5-year survival rate in the Guidelines group was similar to that in the control group (94.2% vs 92.3%).

Conclusion. Surgeons treated more cases of mucosal cancer with nodal metastasis after the introduction of the Guidelines. The long-term oncological outcomes for patients with EGC remained excellent. So far, the Guidelines for the treatment of EGC appear acceptable.

Key words Early gastric cancer · Lymph node metastasis · Gastric cancer treatment guidelines

Introduction

Early gastric cancer (EGC) is defined as invasion confined to the mucosa or submucosa, regardless of the presence of regional lymph node metastasis. In recent years, the incidence of EGC has reached more than 50% of all gastric cancer cases in Japan. Gastrectomy with D2 lymphadenectomy had been firmly accepted as a standard treatment for every stage of gastric cancer since the 1980s [1, 2]. EGC treated with radical surgery has an excellent survival rate, with 5-year survival rates of more than 90% being reported by both Western [3] and Japanese [4] investigators. However, ever since the clinicopathological features of EGC, such as the incidence of lymph node metastasis, were clarified in the late 1990s, gastrectomy with D2 lymphadenectomy for all patients with EGC has come to be considered as an overtreatment [5–8].

The gastric cancer treatment guidelines (Guidelines) were issued by the Japanese Gastric Cancer Association (JGCA) in March 2001 [9, 10]. The Guidelines were designed to provide standard indications for the selection of treatments for gastric cancer according to the clinical stages of the disease (JGCA classification). The Guidelines allowed endoscopic resection and a modified gastrectomy as treatment modalities for EGC, in addition to a standard gastrectomy. Endoscopic treatment can be utilized in patients with a minimal chance of lymph node metastasis. A modified gastrectomy, including limited lymphadenectomy, can be utilized in patients with EGC beyond the inclusion criteria for endoscopic treatment. Because patients with a minimal chance of lymph node metastasis were excluded as candidates for a gastrectomy, Japanese surgeons are interested in whether surgeons are actually facing an increasing number of EGC cases with a greater chance of lymph node metastasis. Furthermore, whether a modified gastrectomy with a reduced extent

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of lymphadenectomy is sufficient treatment for these cases of EGC with a greater chance of lymph node metastasis is also a topic of interest. We retrospectively investigated the clinicopathological characteristics and long-term oncological outcomes of EGC patients who underwent a gastrectomy after the introduction of the Guidelines and compared our results with those obtained in patients treated before the introduction of the Guidelines.

Patients and methods

Patients

Between January 1991 and December 2003, 2218 patients with EGC underwent a gastrectomy with curative intent at the National Cancer Center Hospital, Tokyo. Between March 2001 and December 2003, 696 of these patients underwent a gastrectomy according to the Guidelines. These 696 patients (the Guidelines group) were retrospectively compared with 635 patients (the control group) who had undergone a gastrectomy between January 1991 and December 1995 (before the introduction of the Guidelines). Patients who had undergone a gastrectomy between January 1996 and February 2001 were excluded from this analysis because endoscopic resection and a modified gastrectomy for EGC were frequently performed as investigational treatments during this period. Surgical specimens were examined and scored according to the *Japanese classification of gastric carcinoma* [9]. The vital statistics for all the patients were obtained from the city registry office and the follow-up records. All the patients were followed up for at least 5 years.

Surgical procedures

Before the introduction of the Guidelines, a gastrectomy with D2 lymphadenectomy was performed as a standard treatment for every stage of gastric cancer. After the introduction of the Guidelines, definite recommendations for endoscopic treatment were confined to tumors in the mucosal layer; type I, IIa, or depressed type IIc with no ulcers; well- or moderately differentiated adenocarcinoma; and tumors smaller than 2 cm. A modified gastrectomy was utilized in patients with cT1N0 (stage IA) tumors and cT1N1 (stage IB) tumors less than 2.0 cm in size, excluding patients who fulfilled the criteria for endoscopic resection. The modified gastrectomy allowed a reduced extent of lymphadenectomy, compared with a D2 lymphadenectomy. While the N1 nodes were completely removed, some supra-pancreatic N2 nodes, such as the node along the splenic artery, were excluded from the dissection.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). The significance of the differences in the patients' clinicopathological features and the incidence of lymph node metastasis were determined using the χ^2 test and the Mann-Whitney *U*-test, as appropriate. A 5% significance level ($P < 0.05$) was considered statistically significant. The survival rate was calculated by the Kaplan-Meier method with 95% confidence intervals (CIs), and the hazard ratio was calculated by the Cox proportional hazards model with 95% CIs.

Results

Patient characteristics

The male-to-female ratio in the Guidelines group (1.92: 1) was significantly lower than that in the control group (2.55: 1; Table 1). The median age in the Guidelines group (62 years) was significantly higher than that in the control group (60 years). There was no difference in the distribution of tumor location. The median tumor size in the Guidelines group (30.0 mm) was significantly larger than that in the control group (26.0 mm). The proportion of undifferentiated-type lesions in the Guidelines group (58.0%) was significantly higher than that in the control group (41.7%).

The incidence of lymph node metastasis in patients with mucosal cancers in the Guidelines group (6.5%) was significantly higher than that in the control group (2.6%; Table 2). No difference in the incidence of lymph node metastasis in patients with submucosal cancer was noted between the two groups. The proportion of D2 or greater extended lymphadenectomy in the Guidelines group (207/696; 29.7%) was significantly lower than that in the control group (397/635; 62.5%).

Survival

The median follow-up period in the Guidelines group was 5.5 years, while that in the control group was 7.5 years. During a 5-year follow-up period, 40 patients (5.7%) in the Guidelines group died; 9 of these patients (1.3%) died from recurrence. Thirty-eight patients in the control group (6.0%) died; 6 of these patients (0.9%) died from recurrence. The overall 5-year survival rates were 94.2% (95% CI, 92.4%–96.0%) in the Guidelines group and 92.3% (95% CI, 90.1%–94.5%) in the control group. If the relative risk for death was set at one for patients in the control group, the hazard ratio in the Guidelines group was 0.78 (95% CI, 0.53–1.15) for overall patients. The overall 5-year survival rates for the patients with mucosal cancer were 95.1% (95% CI,

Table 1. Clinicopathological characteristics of patients

	Guidelines (<i>n</i> = 696)	Controls (<i>n</i> = 635)	<i>P</i> value
Sex			
Male/female ratio	1.92	2.55	0.018
Age (years)			
Median	62	60	0.005
Range	31–89	21–86	
Tumor location			0.315
Upper third	88 (12.6%)	69 (10.9%)	
Middle and lower thirds	608 (87.4%)	566 (89.1%)	
Tumor size (mm)			0.05
Median	30.0	26.0	
Range	3–186	2–250	
Depth of invasion			0.121
Mucosa	307 (44.1%)	307 (48.3%)	
Submucosa	389 (55.9%)	328 (51.7%)	
Macroscopic appearance			0.203
Elevated	112 (16.1%)	126 (19.8%)	
Flat	11 (1.6%)	10 (1.6%)	
Depressed	573 (82.3%)	499 (78.6%)	
Histological type ^a			<0.001
Differentiated	292 (42.0%)	370 (58.3%)	
Undifferentiated	404 (58.0%)	265 (41.7%)	

Guidelines, gastric cancer treatment guidelines of the Japanese Gastric Cancer Association

^aAccording to the *Japanese classification of gastric carcinoma* [9]

Differentiated type includes papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated type includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma

Table 2. Incidence of lymph node metastasis according to depth of invasion in the Guidelines and control groups

	Guidelines	Controls	<i>P</i> value
Depth of invasion			
Mucosa	20/307 (6.5%)	8/307 (2.6%)	0.02
Submucosa	78/389 (20.1%)	70/328 (21.3%)	0.671
Overall	98/696 (14.1%)	78/635 (12.3%)	0.334

Guidelines, gastric cancer treatment guidelines of the Japanese Gastric Cancer Association

92.8%–97.5%) in the Guidelines group and 93.7% (95% CI, 91.0%–96.4%) in the control group. The hazard ratio in the Guidelines group was 0.83 (95% CI, 0.44–1.58) for patients with mucosal cancer. The overall 5-year survival rates for the patients with submucosal cancer were 93.5% (95% CI, 91.0%–96.0%) in the Guidelines group and 91.0% (95% CI, 87.9%–94.1%) in the control group. The hazard ratio in the Guidelines group was 0.74 (95% CI, 0.46–1.19) for patients with submucosal cancer.

Discussion

The Guidelines allow endoscopic treatment and a modified gastrectomy for EGC. Candidates for endoscopic treatment include patients with small differentiated-type mucosal cancers. When these tumors were excluded

from the indications for gastrectomy, the tumor size in the Guidelines group was larger and the proportion of undifferentiated-type lesions was greater in the Guidelines group, compared with these parameters in the control group, as expected.

The male-to-female ratio was significantly lower in the Guidelines group than in the control group. Differentiated-type carcinomas are more common among men than among women [11]. Because male patients tend to fulfill the criteria for endoscopic resection more commonly than female patients, more men may have undergone endoscopic treatment. The median age was also slightly higher in the Guidelines group. Considering that differentiated-type tumors, which are occasionally treated using endoscopy, are more common among elderly patients [12, 13], a lower median age in the Guidelines group would not be unexpected. However, the opposite result was obtained. This result might

reflect an increase in the number of elderly patients themselves as a result of the prolonged life expectancy in Japan.

The incidence of lymph node metastasis in mucosal cancers was reported to be 1.2%-3.3% [6, 14–17], and all of these patients with EGC underwent a standard gastrectomy. In the present study, the incidence of lymph node metastasis in mucosal cancers in the control group was similar to those study findings (2.6%), while that in the Guidelines group was significantly higher (6.5%). The reason for this difference is easily interpreted. After the introduction of the Guidelines, endoscopic resection was established as the standard therapy for EGC in patients with a negligible risk of lymph node metastasis; therefore, the incidence of surgically treated patients with lymph node metastasis increased.

The Guidelines recommend D2 gastrectomy only in selected patients. As a result, the proportion of patients undergoing gastrectomy with D2 or greater extended lymphadenectomy was significantly smaller in our Guidelines group (29.7%) than in the control group (62.5%). Nevertheless the 5-year survival rate in the Guidelines group (94.2%) was similar to that in the control group (92.3%) and was also similar to that for patients undergoing gastrectomy with D2 lymphadenectomy in previous reports [18, 19].

In conclusion, surgeons treated more cases of mucosal cancer with lymph node metastasis after the introduction of the Guidelines. The long-term oncological outcomes for patients with EGC remained excellent after the introduction of the modified operation. So far, the Guidelines for the treatment of EGC appear acceptable.

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Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria

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Background: Criteria for endoscopic resection in patients with early gastric cancer (EGC) have been expanded recently by the National Cancer Centre (NCC). This study compared long-term outcomes in patients with EGC who underwent endoscopic treatment according to guideline criteria with those treated according to expanded criteria.

Methods: Baseline and outcome data from patients undergoing curative endoscopic resection for EGC between January 1999 and December 2005 were collected from electronic medical records. Survival time hazard ratios and 95 per cent confidence intervals were calculated using the Cox proportional hazards model.

Results: Of 1485 patients who had a curative resection, 635 (42.8 per cent) underwent resection according to traditional criteria and 625 (42.1 per cent) according to expanded criteria. There was no significant difference in overall survival between the groups.

Conclusion: Patients who have treatment following the expanded criteria have similar long-term survival and outcomes to those treated according to guideline criteria.

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Introduction

In Japan, endoscopic mucosal resection (EMR) has been the treatment of choice for small early gastric cancer (EGC) for the past two decades^{1,2}. Owing to the technical limitations of EMR, traditional indications for endoscopic resection of EGC according to the Gastric Cancer Treatment Guidelines of the Japanese Gastric Cancer Association (JGCA) were restricted to resection of small intramucosal EGCs (smaller than 20 mm) with intestinal-type histology and no ulceration.

The low risk of lymph node involvement in EGC confined to the superficial layers of the submucosa indicated that cure can be achieved by local resection, even of lesions larger than 20 mm, as long as the lesion is removed *en bloc*³. Endoscopic submucosal dissection (ESD) has become established as a technique that allows *en bloc* resection regardless of size. Revised criteria were proposed by the National Cancer Centre (NCC) in Tokyo (from January 1999) to expand the indications for endoscopic

treatment and avoid unnecessary radical surgery, which until recently was the 'gold standard' for larger lesions^{4,5}.

This study compared the long-term outcome of patients with EGC who underwent endoscopic treatment based on either guideline of JGCA criteria or expanded NCC criteria.

Methods

Consecutive patients who had endoscopic resection for EGC between January 1999 and December 2005 were studied. Informed consent was obtained from all patients in accordance with the institutional protocol. The procedure was carried out under conscious sedation using a combination of midazolam and pentazocine. Patients who were assessed histologically as having had a non-curative resection owing to positive lateral margins and/or deep submucosal invasion, regardless of positive vertical margins and/or lymphatic-vascular infiltration and/or diffuse-type histology, and those who had undergone endoscopic

resection as a palliative treatment for advanced cancer were excluded.

Curability was based on the histological criteria for curative endoscopic resection (Table 1) according to the Japanese Classification of Gastric Carcinoma⁶. Pathological assessment of the resected specimen included: size, location, macroscopic appearance, presence of ulceration, histological type, depth of invasion, lymphatic and vascular involvement, and resection margin status. Tumours smaller than 20 mm without ulceration were included in the JGCA criteria group and those larger than 20 mm in the NCC expanded criteria group. Patients with multiple EGCs were analysed as a separate group.

Baseline and outcome data were collected from electronic medical records. Incomplete and missing data were retrieved from different sources such as telephone contact with patients, family and referring physicians, and checked with statistical data kept by the local government registry.

All patients with curative resection who met JGCA criteria were followed up by annual upper gastrointestinal surveillance endoscopy to identify local recurrence and/or metachronous gastric cancer. Patients who met NCC criteria were additionally followed by thoracic and abdominal computed tomography and/or endoscopic ultrasonography every 6 months. Patients were followed from the date of first treatment until 31 July 2007.

Statistical analysis

Survival time was calculated as the interval between the date of the first treatment and the date of death or the last date confirmed as alive for survivors. Survival curves were calculated using the Kaplan–Meier method. To compare overall survival by treatment method, a Cox proportional hazards model was used to estimate hazard ratios and 95 per cent confidence intervals (c.i.). Age, sex and past history of cancer were included as co-variables in the multivariable analyses. All *P* values reported are two sided and *P* < 0.050 was considered statistically significant.

Table 1 Histological criteria for curative endoscopic resection

Factors for no risk of lymph node metastasis	
Intestinal-type histology	
No lymphatic or vascular infiltration	
Intramucosal cancer regardless of tumour size without ulcer finding or intramucosal cancer less than 30 mm in size with ulcer finding or minute submucosal invasive cancer (sm1) less than 30 mm in size	
Factors for resection margin	
Tumour-free horizontal margin	
Tumour-free vertical margin	

Statistical analyses were performed with SAS[®] software version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

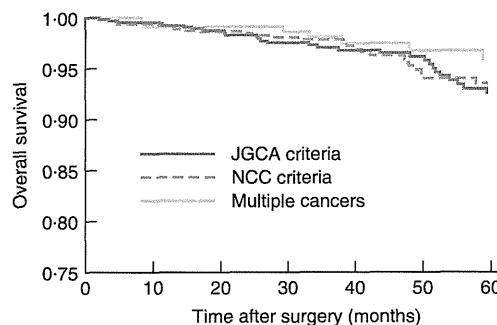
Some 1786 lesions were resected curatively among 1485 patients; 635 patients (42.8 per cent) were treated according to the guideline of JGCA criteria and 625 (42.1 per cent) in accordance with the expanded NCC criteria; 225 patients (15.2 per cent) had multiple EGCs with both criteria. Baseline characteristics by treatment allocation are shown in Table 2.

Follow-up was complete for all 1485 patients, with a median observation period of 44.1 months. During follow-up, 77 patients died (5.2 per cent). Only one patient treated according to JGCA criteria died from metachronous invasive gastric cancer, which was detected 5 years later. Locally recurrent gastric cancer was found in another patient who underwent piecemeal endoscopic resection. This patient underwent ESD for local recurrence 18 months after the first endoscopic resection and was alive with no evidence of recurrence after 57 months. There was

Table 2 Baseline patient characteristics by treatment group

	JGCA criteria (n = 635)	NCC criteria (n = 625)	Multiple cancers (n = 225)
Mean age (years)	66.4	66.5	68.6
Men	479 (75.4)	505 (80.8)	180 (80.0)
Past history of cancer	154 (24.3)	87 (13.9)	95 (42.2)
Mean tumour size (mm)	10.8	23.8	12.4

JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre.



No. at risk	0	10	20	30	40	50	60
JGCA criteria	635	631	584	455	346	264	186
NCC criteria	625	621	559	433	314	242	156
Multiple cancers	225	223	210	180	156	126	89

Fig. 1 Survival by treatment group. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre

Table 3 Hazard ratio for all-cause mortality according to treatment group

	No. of deaths	5-year survival rate (%)	Hazard ratio	
			Crude	Adjusted*
JGCA criteria	36	92.4	1.00	1.00
NCC expanded criteria	31	93.4	0.93 (0.57, 1.50)	1.10 (0.67, 1.81)
Multiple cancers	10	95.6	0.63 (0.31, 1.26)	0.46 (0.23, 0.94)

Values in parentheses are 95 per cent confidence intervals. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre. *Multivariable Cox proportional hazards model, adjusted for age, sex and past history of cancer.

no significant difference in the rate of local and/or systemic recurrence between the JGCA and the NCC groups.

Survival curves are shown in *Fig. 1*. The 5-year survival rate was 92.4 per cent in the JGCA group, 93.4 per cent in the NCC group and 95.6 per cent among those with multiple cancers. There was no significant difference in overall survival (*Table 3*). In multivariable analysis, the hazard ratio for survival of patients in the NCC group compared with those in the JGCA group was 1.10 (95 per cent c.i. 0.67 to 1.81).

Discussion

Radical surgery with complete removal of first- and second-tier lymph nodes is accepted as a standard treatment for patients with EGC. A 5-year survival rate of around 90 per cent has been achieved in oriental and Western patients^{7–9}. In patients with cancer limited to the mucosa, the incidence of lymph node metastasis is less than 3 per cent. This risk increases to 20 per cent when the cancer invades the submucosa¹⁰.

Radical surgery may not be the optimal treatment approach in all patients with EGC because it carries a significant risk of morbidity and mortality, and is associated with a significant reduction in quality of life^{11–13}. Patients with no risk of lymph node metastasis can be treated safely by endoscopic resection¹⁴.

Accepted indications for EMR of EGC have been (1) well differentiated elevated cancers less than 2 cm in diameter and (2) small (maximum 1 cm) depressed lesions without ulceration. These indications were established because of the technical limitations of EMR. In larger lesions, EMR has a high risk of recurrence as a result of incomplete resection when piecemeal EMR is used for larger lesions¹⁵. Specimens obtained by piecemeal EMR are difficult to analyse and there is a high risk of inadequate histological staging¹⁶. From a histological point of view, *en bloc* removal should be considered essential for endoscopic resection of larger lesions to ensure accurate histological staging. The treatment strategy for EGC has

been revolutionized recently by the ESD procedure. This method is superior to other endoscopic techniques used for EGC as it makes *en bloc* resection possible, allowing precise histological staging and minimizing recurrence risk compared with standard EMR techniques¹⁷.

Kojima and colleagues¹⁸ have reviewed the outcomes of EMR from 12 major institutions in Japan. Long-term outcomes after EMR for small differentiated mucosal EGC less than 2 cm in diameter have been reported to be comparable to those following gastrectomy¹⁹, but the long-term outcome of endoscopic resection of large EGCs has not been reported.

The present study has demonstrated that there is no difference in 5-year survival and local and/or systemic recurrence rates between patients treated according to JGCA or NCC criteria. The hazard ratio for overall survival showed no significant difference between the two groups.

Final staging can be carried out accurately only by formal histological analysis, especially with regard to potential lymphovascular infiltration. Therefore, *en bloc* resection is a prerequisite for accurate staging and prediction of a patient's risk of lymph node metastasis.

Expanded NCC criteria for patients with EGC are safe and practicable. As a result of the ability to achieve *en bloc* resection by ESD, more patients may benefit from endoscopic resection, further reducing the need for radical surgery.

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