Prognosis of Patients with Gastric Carcinoma Treated in Remote Island Hospitals in Japan: A Multivariable Analysis

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Abstract. *Background: Treating gastric cancer in remote island hospitals remains a major clinical challenge. Factors affecting prognosis of patients treated in general hospitals are still at large. We sought to determine the characteristics of gastric cancer in the Amamiooshima (Amami) archipelago of Japan and also evaluated the independent prognostic factors by the Cox regression analysis. Materials and Methods: A total of 125 patients treated in four sister hospitals in the Amami were analyzed. Results: The median age of patients with resection was 74 years and almost 85% patients had diffuse type of cancer. The 5-year overall survival was 34% for all patients and 58% for those who had a resection. Among the several clinicopathological factors, operation method (distal vs. total gastrectomy), splenectomy, lymphatic and venous invasion, T-stage, metastatic lymph node (MLN) size n-stage and UICC N-stage had significant impact on survival. Only MLN size and intraoperative blood loss had independent effect on survival by multivariable analysis. Conclusion: Improved perioperative care may yield a reasonable patient survival in elderly patients with gastric carcinoma treated in remote hospitals. Restricting amount of intraoperative blood loss may further improve the patient prognosis and MLN size may serve as a new metric to stage gastric cancers.*

Deaths from gastric carcinoma constitute a major share of cancer-related deaths worldwide (1, 2). In Japan, gastric carcinoma is still one of the leading causes of malignancy-related deaths (3). Patients with localized and early-stage diseases have excellent prognoses after curative resection; but the prognosis for patients with advanced disease remains dismal (4). In general, the prognosis of patients with gastric carcinoma treated in Japan is better than their counterpart in the Western world. In Japan, most of the published articles are from either specialized centers of university hospitals or from cancer specialty hospitals. However, it remains unknown whether a similar outcome could be achieved in general hospital settings in Japan.

Amamiooshima (Amami) archipelago is a cluster of small islands situated in the East China sea and is inhabited by approximately 130 thousand people. The people of the Amami archipelago have unique cultural heritage and distinct food habits when compared with the mainland. It has been reported that the incidence of gastric cancer in Japan is higher in the Niigata prefecture due to high intake of salted foods and rice, whereas it is lower in the southern islands where people use to consume less salted foods (5, 6). However, the characteristics of gastric cancer in the southern part of Japan remain unknown.

A significant percentage of the world populations live in remote islands and access to the modern medical facilities often remains difficult. From the perspective of remote location, the disease pattern, diagnosis and management of gastric carcinoma remain to be different from those treated in the mainland specialized hospitals. To date, several prognostic factors are reported in gastric cancer patients and new prognostic parameters are coming out which will help the clinicians to tailor the treatment strategy according to the need of their patients. In this study, the characteristics of gastric cancer in the Amami archipelago were determined and the independent prognostic factors by the Cox regression multivariable analysis were evaluated.

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Materials and Methods

Between 1998 and 2005, among 138 patients with histologically confirmed gastric carcinoma at any of the four hospitals in Amamiooshima Tokushukai hospitals (Naze, Setouchi, Kikai and Tokunoshima), 125 patients had a complete follow-up data and were included in this study. Of these patients, 52 (42%) were women and 73 (58%) were men; their ages ranged from 39 to 95 years (median 77). The ethical committee of the Tokushukai Medical Incorporation, Tokyo, Japan, approved the study protocol following a stringent review of the study protocol.

All patients underwent routine check-ups including complete blood chemistry, full blood counts, tumor markers, a complete heart, lung and liver function test. Also, patients underwent diagnostic imaging tests including a routine CT examination. In suspected cases of distant metastatic diseases, MR imaging and bone scintigraphy were performed. In general, patients with intramucosal tumors underwent endoscopic mucosal resection (EMR) and those with advanced disease underwent surgical resection of the tumor. Operations were judged to be curative when there was complete removal of the disease macroscopically at operation and the resection margins were histologically free of cancer cells. A D2 lymph node dissection was the standard procedure, but, it depended largely on the patient's general condition. All dissected lymph nodes and resected specimens were subjected for the pathological examination. Histologic evaluation followed the Japanese General Rules for Gastric Cancer Study (7). Histologic differentiation was classified according to the Lauren's classification. Post-operative chemotherapeutic drugs were rarely prescribed, as most of the patients were elderly with poor general condition. A retrospective database was constructed with information collected from the patient card. An update inquiry about the present status of all surviving patients was done over telephone or by sending a respond post-card in December 2005.

All harvested lymph nodes were sliced at several points and stained by hematoxylin and eosin method. The number of metastatic lymph nodes (MLNs) was counted for each patient and the MLN containing the largest metastatic tumor was selected for measurement. All MLNs were evaluated under a conference light microscope by two individual authors (MT and DKD) with no knowledge of patient outcome. The microscopic size of the metastatic tumor was determined by using a measure incorporated in the eyepiece of the microscope. When more than one distinct metastatic deposit were present, the sum of all metastatic deposits was considered as the MLN size. The MLN size stage has been designated as n-stage and the UICC lymph node stage as N-stage throughout this article.

Statistical analysis. Survival was measured from the date of operation or diagnosis of the disease and was estimated using the Kaplan-Meier method and the log-rank test was used to determine statistical differences between groups. Correlation between continuous variables was evaluated by the Spearman rank correlation test. A p-value <0.05 was considered to be significant by the log-rank test.

Results

In 125 patients, the tumor location was as follows: lower third in 41 (33%) cases, middle third in 32 (28%) cases and in upper third in 49 (39%) cases. Endoscopic mucosal resection (EMR) was performed in 12 (10%) cases, gastric resection in 68 (54%) cases and 45 (36%) patients underwent a palliative treatment. Among the 68 patients with a gastric resection, only 10 (15%) patients had intestinal type of cancer and 58 (85%) patients had diffuse or mixed type of cancer. The median number of dissected lymph nodes was 17 (range 1 to 97) and the median number of MLN was 4 (range 1 to 35). The MLN size ranged from 0.2 mm to 33 mm (median 7.5). According to the Spearman rank correlation test, there was a significant ($p=0.0132$, $r^2=48.9$) direct correlation between the number and size of MLNs (data not shown). The cut-off point of MLN size n-stage was determined according to the criterion as stated in our previous article (7). According to this criterion, patients with MLN were divided into two prognostic groups: n1 (MLN size $\leq$7 mm) and n2 (MLN size $\geq$8 mm). Among the 68 patients with gastric resection, in two patients the lymph node status could not be identified and, therefore, 66 patients were evaluated in the subgroup analyses. Of 66 patients with gastric resection, 39 (59%) patients were node negative and 27 (41%) patients had metastasis in regional LNs. According to our criterion of MLN size n-stage: 13 (48%) patients had n1 disease and 14 (52%) patients had n2 disease.

In 125 patients, the 5-year overall survival rate was 34%; it was 100% for the 12 patients with EMR, 52% for the 68 patients with gastric resection and only 3% for the 45 patients with palliative treatment (Figure 1A). The relationship between the clinicopathological factors and patient survival are shown in Table I. Among the several clinicopathological factors, operation method (distal *vs.* total gastrectomy), splenectomy, lymphatic and venous invasion, T-stage, MLN size n-stage and UICC N-stage had significant impact on survival in the univariate analysis. Patients with total gastrectomy had worse outcome than those who underwent a distal gastectomy operation. Patients with gastric resection and splenectomy operation had poor outcome. Patients with lymphatic or venous invasion had significant poor overall survival. The 1-year, 3-year and 5-year overall survival of patients with T1+T2 diseases and those with T3+T4 diseases were 84.5%, 83.2% and 63.0% and, 58.3%, 36.3% and 36.3%, respectively ($p=0.0007$). Both MLN size n-stage and UICC N-stage stratified patients into significant prognostic groups as shown in Figure 1 (B and C). Subgroup analyses showed that patients with N1 disease of the UICC N-stage could be further subdivided into prognostic groups by the MLN size n-stage classification ($p=0.0452$), whereas patients with both the n1 and n2 diseases could not be divided into prognostic groups by the UICC n-stage (data not shown).

Multivariable analysis. Independent prognostic factors were evaluated by a stepwise multivariable Cox regression analysis. According to this analysis, only MLN size n-stage and amount of intra-operative blood loss were independent predictors of survival. Operation time and UICC N-stage had a trend of

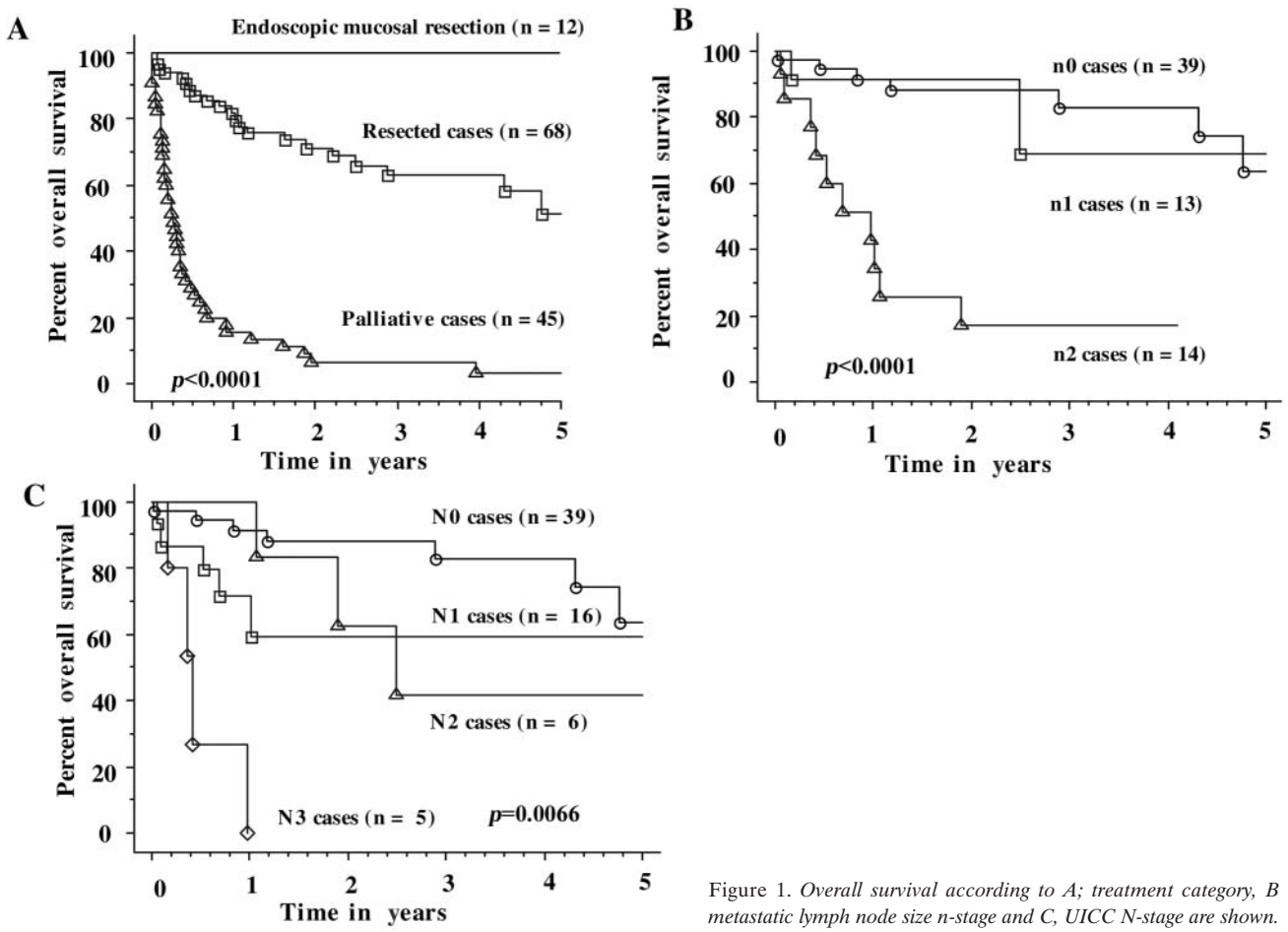

Figure 1. *Overall survival according to A; treatment category, B metastatic lymph node size n-stage and C, UICC N-stage are shown.*

independent impact on patient survival, however, there was no statistical significance (Table II).

Discussion

Gastric carcinoma is the second most frequent malignancy in the world after lung carcinoma (2). Despite a gradual drop in the incidence of gastric carcinoma worldwide, the absolute number of patients with gastric carcinoma is still increasing in Japan because of an increasing number of aged population (3). Also, in the Amami archipelago, the death rate from gastric carcinoma is gradually increasing in recent years (personal communication from the City Office, Naze, Japan). The overall 5-year survival in Amami was 36% in all cases and 58% in patients who underwent a resection. The survival rates seem to be slightly lower when compared with the reports from the specialized institutions in Japan, but are still better than those reported from the Western institutions (8, 9). This apparently lower survival could be attributable to an increasing number of elderly patients treated in these island hospitals in Amami archipelaogo. Indeed, the median age of patients with gastric carcinoma was 77 years and those who underwent gastric resection it was 74 in this study. From this perspective the survival is comparable to those of the specialized institutions in Japan (10). Most of the deaths were due to senility and there were only a few post-operative complications; only two patients died from these complications.

Despite the fact that our understanding of the carcinogenetic process of gastric carcinoma has grown exponentially in the last 20 years, the exact mechanism of gastric carcinogenesis remains unknown. The most probable sequel of gastric cancer formation from normal gastric mucosa includes acquisition of *Helicobacter pylori* infection, consumption of dietary carcinogen, chronic gastritis followed by atrophic gastritis, intestinal metaplasia and tumor formation (11). This pattern is more common in elderly people and includes intestinal type of cancer in the lower portion of stomach. Surprisingly, in this study population with a median age of 77 years, almost 85% patients had diffuse type of cancers and the location of the cancer was highest in upper portion of the stomach. It seems that a different

Table I. *Univariate analysis of prognosis according to different clinicopathological factors.*

Parameters	1-year survival	3-year survival	5-year survival	*p*-value
Age				
<74(34)	77.1	59.8	37.4	0.2514
>74(34)	79.9	68.1	68.1	
Gender				
Male (41)	84.7	84.7	54.6	0.7880
Female (27)	67.2	67.2	50.4	
Operation method				
Distal gastrectomy (37)	87.7	75.5	67.2	0.0039
Total gastrectomy (31)	67.8	51.6	0.00	
Splenectomy				
Yes (6)	33.3	0.00	0.00	0.0001
No (62)	83.7	70.3	57.7	
Operation time (min)				
<310 (34)	76.2	63.7	58.1	0.6919
>310 (34)	79.2	61.2	49.0	
Operative blood loss (ml)				
<530 (34)	78.4	72.8	72.8	0.1950
>530 (34)	77.6	60.3	34.9	
Lauren's classification				
Intestinal type (10)	77.8	77.8	77.8	0.2673
Diffuse + mixed type (58)	78.5	64.8	43.2	
Lymphatic invasion				
Negative (43)	91.9	85.4	64.9	0.003
Positive (25)	58.1	34.9	34.9	
Venous invasion				
Negative (55)	87.3	76.4	59.5	<0.0001
Positive (13)	45.5	30.3	30.3	
T-stage				
T1 + T2 (42)	84.5	83.2	63.0	0.0007
T3 + T4 (26)	58.3	36.3	36.3	
MLN size n-stage*				
n0 (39)	91.4	88.0	63.9	<0.0001
n1 (13)	91.7	68.8	68.8	
n2 (14)	51.4	17.1	0.00	
UICC N-stage				
N0 (39)	91.4	88.0	63.9	0.0066
N1 (16)	100.0	41.7	41.7	
N2 +N3 (11)	70.7	25.3	25.3	

*MLN=metastatic lymph node, numbers in the parentheses are number of patients.

Table II. *Multivariable analysis of independent risk factors.*

Parameters	Risk ratio (95% CI)	*p*-value
Age (years)	0.960 (0.906 – 1.017)	0.1685
Gender	0.453 (0.103 – 1.584)	0.4530
Operative method	2.651 (0.540 – 13.018)	0.2299
Splenectomy	0.096 (0.007 – 1.238)	0.0724
Operation time (min)	0.989 (0.976 – 1.001)	0.0641
Operative blood loss (ml)	1.002 (1.000 – 1.004)	0.0443
Lauren's classification	0.099 (0.006 – 1.614)	0.1044
Lymphatic invasion	0.708 (0.250 – 2.001)	0.2617
Venous invasion	2.002 (0.596 – 6.726)	0.1685
T-stage	2.002 (0.596 – 6.726)	0.1685
MLN n-stage	3.831 (1.095 – 13.399)	0.0355
UICC N-stage	3.169 (0.933 – 10.761)	0.0645

MLN=metastatic lymph node, CI=confidence interval.

mechanism than the *Helicobacter pylori* infection is responsible for this high prevalence of diffuse type of cancer in Amami.

The overall prevalence of diffuse type of gastric cancer and cardiac cancer are increasing in the Western world, as well as in Japan (12). The food habit, culture and also body stature of the people of the Amami archipelago are different than those of the Japan mainland and in many aspects they have similarities with the Western populations in regard to body stature. It has been well demonstrated that somatic, as well as germline mutation of the *E-cadherin* gene plays a pivotal role in the formation of diffuse type of gastric cancer (13, 14). Therefore, whether a similar mechanism of carcinogenesis is responsible for an increased prevalence of diffuse type of gastric caner in this archipelago inhabited by indigenous people, remains to be identified.

Surgical resection is the mainstay of treatment for patients with gastric carcinoma. A curative resection with extensive lymph node dissection incurrs intra-operative blood loss, necessitating blood transfusion as an inevitable procedure related to surgery. To date, there are several reports indicating that increase blood loss and transfusion impedes an adverse effect on prognosis of patients with gastric resection (15-17). In line with the results of previous studies, blood loss became a significant independent predictor of survival in this study. The possible mechanisms of adverse effect of increase intra-operative blood loss and blood transfusion would be an immunosuppressant effect of BT and also the presence of multiple growth factors especially those derived from platelets during blood storing. It has been thought that transfusion of packed red blood cells rather than whole blood may avoid the adverse effects of BT. Therefore, the attendant risk of BT could be reduced by using PRBCs rather than whole blood and by improving peri-operative patient care.

Regional lymph node status remains one of the most important prognostic factors in gastric carcinoma (18). An adequate lymph node dissection is a prerequisite for proper lymph node staging and tailoring treatment in individual patients (19). In general, an extensive lymph node dissection is practiced in most of the major hospitals in Japan, and the average number of lymph nodes harvested at operation ranges from 20 to 42. The picture might be different in general hospitals where a large number of elderly patients are treated with caution to avoid dire post-operative complications related to extensive LN dissection. In this study the median number of harvested lymph nodes was only 17, which is near to the lowest requirement for an

adequate LN staging by the UICC classification system. The results of this study indicate that a down staging occurred in the UICC classification and patients with UICC N1 disease could be further stratified into prognostic groups by the MLN size n-stage classification. As previously shown, the MLN size could serve as a useful metric to classify lymph node stage parameter (20 - 24). Also in this study, the MLN stage n-stage had the strongest independent predictive value for prognosis of patients with gastric carcinoma. Further studies are necessary to determine whether the MLN size n-stage alone or in combination with the MLN number or ratio (metastatic/dissected) could be a useful parameter for classification of the lymph node stage in patients with gastric cancer.

In conclusion, the results of this study showed an increased prevalence of diffuse type of gastric cancer in people living in the Amami archipelago. Precaution regarding intra-operative blood loss may further improve survival of elderly patients treated in these remote island hospitals. MLN size may serve as a useful tool to classify patients with lymph node metastasis.

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