



Long-Term Survival in Japanese Patients with Far Advanced Carcinoma of the Stomach

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Among 1,220 Japanese patients with gastric carcinoma who had undergone resection in the Department of Surgery II, Kyushu University Hospital, Fukuoka, Japan from 1965 to 1980, there were 432 (35.4%) with far advanced carcinoma, designated as a lesion with factors such as peritoneal dissemination, hepatic metastasis, widespread nodal involvement extending to tertiary (hepatoduodenal, retropancreatic, and mesenteric) or quaternary (middle colic and paraaortic) nodes, or direct invasion to adjacent organs. The overall 5-year survival rate in these 432 patients was 10.2%. The 5-year survival rate in patients with a single factor was 16.3%, being significantly higher than the 2.8% or less in cases with more than 2 factors ($p < 0.01$). Patients with tertiary nodal involvement or directly invaded organs alone survived at a rate of 26.1% and 21.8% in the 5-year follow-up, respectively. Radical procedures such as extensive lymphadenectomy and combined resection of the invaded organs further lengthened the survival time. The 5-year survival rates were less than 10% in patients with other factors, singly or more than 2 factors in combination. There appear to be 2 subgroups in whom the rates of survival differ: potentially curable and noncurable patients. More intensive therapeutic regimens corresponding to both groups need to be considered.

Despite advances in surgical management, including operative techniques and postoperative care, a large number of patients with gastric carcinoma undergo a palliative operation. In such cases, the 5-year survival rate remains around 10% or less in Western countries [1-3], and also in Japan, where a remarkable rise in the outcome has occurred since the 1970's [4, 5].

Peritoneal dissemination, hepatic metastasis, widespread nodal involvement, and direct invasion to adjacent organs are present at a late stage of the disease and greatly influence the prognosis [4, 5]. Since far advanced carcinoma includes various types of disease with different prognostic factors, a detailed analysis of the prognosis, in terms of the combination of these factors, may eventually lead to a prolongation of survival in such patients.

Prognostic factors in cases of far advanced carcinoma of the stomach were studied from the standpoint of survival following resection, and our observations are reported herein.

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Material and Methods

This study was based on a consecutive series of 1,220 Japanese patients with gastric carcinoma who had undergone resection in the Department of Surgery II, Kyushu University Hospital, Fukuoka, Japan during the 16 years from 1965 to 1980. These 1,220 were classified into 4 groups according to the histological staging system outlined by the Japanese Research Society for Gastric Cancer [6]. The incidence and the cumulative 5-year survival rates corresponding to the stage are shown in Table 1. There were 432 (35.4%) patients with far advanced carcinoma, classified as stage IV and designated as a lesion with factors such as peritoneal dissemination (P), hepatic metastasis (H), widespread nodal involvement extending to tertiary or quaternary lymph nodes (n3 or n4), and direct invasion to adjacent organs: carcinoma extending beyond the serosa and infiltrating to the neighboring organs (si). The tertiary lymph nodes can be equated, for the most part, to those in the hepatoduodenal ligament, retropancreatic area, and mesenteric root. The quaternary lymph nodes are those around the middle colic artery and the abdominal aorta. Since these are not completely removable by means of standard lymphadenectomy [7, 8], the determination of quaternary nodal involvement was usually based on macroscopic findings. These 432 cases, classified as being in stage IV, were selected for further study.

To evaluate the influence of each factor on survival, 4 categories were prepared: category A, with a single factor ($n = 225$); category B, with 2 factors ($n = 140$); category C, with 3 factors ($n = 44$); and category D, with 4 factors ($n = 4$). The other 19 patients were excluded from the study since there was a lack of data on pathology and prognosis. The types of resection are shown in Table 2. Intraoperative radiotherapy was not given to these patients.

The survival rates were calculated by the actuarial life table method and the equalities of the survival distributions for the patient groups were tested by the generalized Wilcoxon test and the Cox-Mantel test. Differences were considered to be significant when both p values by the 2 analytical methods were less than 0.05. Computations were carried out using the statistical package, BMDP 1L [9], on an IBM system 4341 computer.

Table 1. Incidence and survival for patients with gastric carcinoma.

Stage	No. of patients, (%)	5-year survival (%)
I	330, (27.0)	93.3
II	109, (8.9)	80.0
III	349, (28.6)	48.1
IV	432, (35.4)	10.2
Total	1,220	49.9

Table 2. Types of resection in 432 patients with far advanced gastric carcinoma.

Type of resection	No. of patients ^a
Distal gastrectomy	180 (39)
Proximal gastrectomy	11 (4)
Total gastrectomy	230 (146)
Total gastrectomy for carcinoma in the remnant stomach	4 (2)
Pancreatoduodenectomy	7 (7)

^a Numbers in parentheses indicate the number of patients in whom combined resection of other organs was performed.

Definitions concerning curative and noncurative resections and classification of lymph nodes were based on the general rules outlined by the Japanese Research Society for Gastric Cancer [6].

Results

Among 432 patients classified as stage IV, there were 81 (18.8%) who underwent curative resection and 351 (81.2%) subjected to noncurative resection. The 5-year survival rates were 28.9 and 5.8%, in patients with curative and noncurative resections, respectively.

Postoperative survival curves, according to each category, are illustrated in Fig. 1. The 5-year survival rates were 16.3%, 1.5%, and 2.8% in categories A, B, and C, respectively. The survival rate of category A was high, with a statistical difference compared with category B ($p < 0.01$) and category C ($p < 0.01$). All 4 patients in category D died within 2 years after resection.

Category A of stage IV carcinoma includes 5 single factors. The postoperative survival rates are summarized in Table 3. The survival rates at 1, 3, and 5 years for those with n3 component alone were 78.9%, 34.2%, and 26.1%, respectively. The rates for individuals with si component alone were 62.1%, 31.5%, and 21.8%, respectively. On the other hand, the 3-year survival rates in patients with n4, H, or P factors alone were 9.0%, 7.1%, and 3.3%, respectively, and only 9.0% of patients with n4 factors alone survived 5 years after resection. There were significant statistical differences comparing the n3 group to the n4, H, or P groups ($p < 0.01$) and comparing the si group to the n4, H, or P groups ($p < 0.01$).

Gastrectomy with complete removal of invaded organs was carried out in 45 (54.2%) of 83 patients with si component alone. Gastrectomy with sufficient lymphadenectomy to complete removal of primary, secondary, and tertiary nodes was performed in 27 (49.0%) of 55 patients with the n3 component alone. The survival curves are shown in Fig. 2. In the si group (Fig. 2A), the 5-year survival rate was 26.8% in cases of

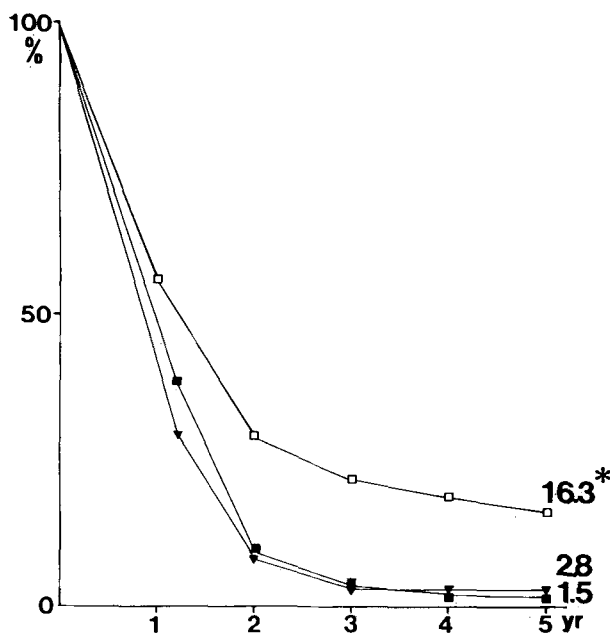


Fig. 1. Postoperative survival curves in categories, A, B, and C. Ordinate: Survival rate (%), Abscissa: Postoperative time (yr), □-□: Category A (225 cases), ■-■: Category B (140 cases), ▼-▼: Category C (44 cases). There are statistical differences when comparing category A with category B ($p < 0.01$) and category C ($p < 0.01$).

Table 3. Survival rate in cases of far advanced gastric carcinoma (category A).

Factors	No. of patients	Survival rate (%)				
		1	2	3	4	5
n3	55	78.9	42.2	34.2	30.1	26.1 ^a
si	83	62.1	40.7	31.5	23.3	21.8 ^a
n4	39	35.2	13.5	9.0	9.0	9.0
H	18	28.2	7.1	7.1	7.1	-
P	30	40.0	6.7	3.3	3.3	-
Total	225	55.9	29.0	22.5	18.4	16.3

^a Statistical differences compared with the other 3 groups ($p < 0.01$: n3 versus n4, H, P; si versus n4, H, P).

complete removal of invaded organs, being significantly higher than the 16.9% in patients undergoing gastrectomy alone or with incomplete removal of invaded organs ($p < 0.05$). In the n3 group (Fig. 2B), the rates were 29.6% in patients for whom a sufficient lymphadenectomy had been done and 17.3% in those for whom the lymphadenectomy was not sufficient.

Among patients classified as categories B and C, 7 groups with over 10 patients in each group were selected and the survival rates summarized in Table 4. In category B, noncurative resection was performed in the majority of cases, except for 3 with si plus n3 components. The 3-year survival rates were less than 10% in each group. Five percent of patients with si plus n4 components and 7.1% of those with P plus n4 components survived 5 years. The prognosis for those classified as category C was poor and all died within 3 years after resection.

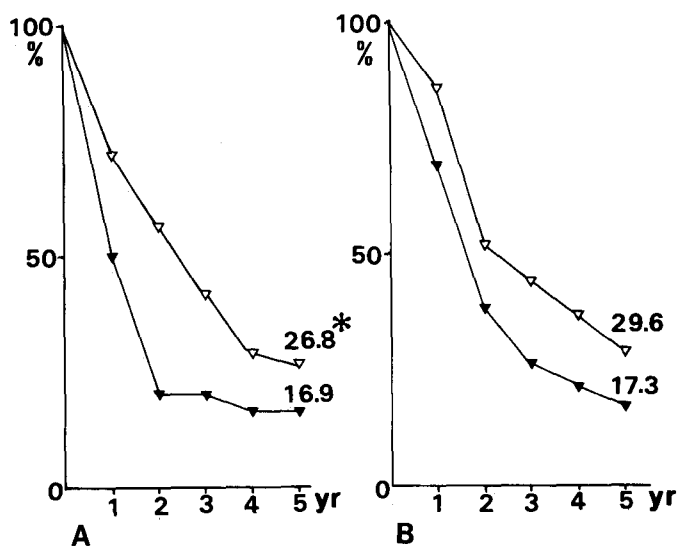


Fig. 2. Postoperative survival curves in patients with si and n3 component, singly. Ordinate: Survival rate (%), Abscissa: Postoperative time (yr). A. Si group. ∇ - ∇ : Gastrectomy with complete removal of invaded organs, 45 cases; \blacktriangledown - \blacktriangledown : Gastrectomy alone or gastrectomy with incomplete removal of invaded organs, 43 cases. There is a statistical difference compared with those undergoing gastrectomy alone or gastrectomy with incomplete removal of invaded organs ($p < 0.05$). B. n3 group. ∇ - ∇ : Gastrectomy with sufficient lymphadenectomy, 27 cases; \blacktriangledown - \blacktriangledown : Gastrectomy with insufficient lymphadenectomy, 28 cases.

Table 4. Survival rate in cases of far advanced gastric carcinoma (categories B and C).

Factors	No. of patients	Survival rate (%)				
		Yr	1	2	3	4
Category B						
si, n3	24	37.5	16.7	4.2	4.2	-
si, n4	26	49.7	10.4	5.2	5.2	5.2
P, si	40	43.9	5.5	2.7	-	-
P, n4	14	21.4	7.1	7.1	7.1	7.1
H, n3	15	26.7	-	-	-	-
Total	140	37.8	8.5	3.1	2.3	1.5
Category C						
P, si, n3	11	63.6	18.2	-	-	-
P, si, n4	16	31.3	6.3	-	-	-
Total	44	29.6	8.4	2.8	2.8	2.8

Combination groups comprising less than 10 patients were not included.

Discussion

The criteria for staging of gastric cancer formulated by the Japanese Research Society [6], outline the degree of metastases or invasion and closely reflect patient survival time [4]. This classification has also been applied to clinical trials performed by Western surgeons [10].

According to reports in Japan, the 5-year survival rates following resection in patients with far advanced carcinoma classified as stage IV ranged from 2.2% to 19.7% [4, 11], the average of which is in close agreement with the rates obtained in this study. As a result of a detailed analysis, however, 2

subgroups with different rates of survival are included in patients with stage IV carcinoma: one group with a 5-year survival rate of over 20% (potentially curable) and the other group with a 5-year survival of less than 10% (noncurable). The former group included patients in category A with tertiary nodal involvement alone or direct invasion to adjacent organs alone. The latter group were those patients in categories A, B, C and D with peritoneal dissemination, hepatic metastasis, and quaternary nodal involvement, either alone or in various combinations.

In potentially curable patients, radical procedures such as extensive lymphadenectomy and combined resection of invaded organs led to a substantial increase in survival time. The efficacy of radical operation for patients with tertiary nodal involvement and those with direct invasion to adjacent organs has been reported [7, 12, 13]. In light of these findings, the extent of surgical repair seems to influence the prognosis. Efforts to remove all the carcinoma, including metastatic lesions, were, however, unsuccessful in patients with involvement of the tertiary lymph node plus adjacent organs. These results indicate the limitations of curative surgery for far advanced carcinoma and the urgent need for adjuvant therapy. The cooperative study group of surgical adjuvant chemotherapy for gastric cancer in Japan emphasized the effectiveness of postoperative long-term combination chemotherapy with mitomycin C plus Tegafur® (N1-(2'-tetrahydrofuryl)-5-fluorouracil) [11]. Therapy with total-body hyperthermia combined with anticancer chemotherapy has been recently advocated [14]. If such intensive therapeutic regimens are prescribed after radical excision, a prolongation of survival in patients with directly invaded organs and/or tertiary nodal involvement may be feasible.

On the other hand, there are reports of the therapeutic significance of palliative gastrectomy, not only in patients with direct invasion of adjacent organs [3], but also in those with liver metastases [15] or peritoneal dissemination [16]. These findings indicate that palliative resection may be effectual in prolonging survival as well as in the alleviation of symptoms, although results were not satisfactory in terms of long survival. The trend is encouraging because it is only surgery which carries any hope of cure. Takagi et al. [17] recommended en bloc removal of metastatic lesions such as the stomach, neighboring organs, and all regional lymph nodes including paraaortic nodes for patients with far advanced carcinoma. Such an approach warrants further attention.

Résumé

Parmi 1,220 japonais atteints de cancer de l'estomac qui ont subi une résection dans le Département de Chirurgie II de l'hôpital Universitaire Kyushu, Fukuoka, Japan de 1965 à 1980, 432 (35.4%) présentaient des lésions avancées qu'il s'agisse de dissémination péritonéale, de métastases hépatiques, d'une extension ganglionnaire importante intéressant les groupes tertiaires (hépatoduodénal, rétro-pancréatique, et mésentérique) ou quaternaires (coliques moyens et paraaortiques) ou encore l'invasion directe d'organes voisins. Le taux de survie totale à 5 ans de ces 432 malades a été de 10.2%. Ce taux a été de 16.3% en présence d'un seul des facteurs et 2.8% ou moins en présence de plus de 2 facteurs ($p < 0.01$). Le taux de survie à 5

ans fut respectivement de 26.1% et de 21.8% selon qu'existait un envahissement ganglionnaire tertiaire ou l'invasion isolée d'un organe voisin. Les techniques radicales: lymphadénectomie élargie et résection combinée des organes envahis sont suivies d'un allongement du temps de survie. Les taux de survie à 5 ans furent inférieurs à 10% chez les malades atteints d'autres facteurs isolés ou supérieurs à deux. Il apparaît ainsi que dans le cancer de l'estomac deux sous-groupes, dont le temps de survie est différent, sont à distinguer: les malades potentiellement curables et les malades incurables. Il est donc nécessaire de mettre au point des méthodes thérapeutiques efficaces en fonction des 2 groupes individualisés.

Resumen

Entre 1,220 pacientes japoneses con carcinoma gástrico sometidos a resección en el Departamento de Cirugía II, Hospital de la Universidad de Kyushu, Fukuoka, Japan entre 1965 y 1980, hubo 432 (35.4%) con carcinoma avanzado, entendiéndose como tal una lesión con hallazgos tales como diseminación peritoneal, metástasis hepáticas, extensión ganglionar amplia hasta los ganglios terciarios (hepatoduodenales, retropancreáticos, y mesentéricos) o cuaternarios (cólicos medios y para-aórticos), o invasión directa de órganos adyacentes. La tasa global de supervivencia a 5 años en estos 432 pacientes fue 10.2%. La tasa de supervivencia a 5 años en pacientes con uno solo de tales hallazgos fue 16.3%, que es significativamente mayor que la de 2.8% o menos en pacientes con más de 2 de tales hallazgos ($p < 0.01$). Los pacientes con invasión ganglionar terciaria o con invasión directa de órganos solamente, sobrevivieron a una tasa de 26.1% y 21.8%, respectivamente, en el seguimiento a 5 años. Procedimientos radicales tales como la linfadectomía amplia y la resección combinada de los órganos afectados resultó en prolongación del periodo de supervivencia. Las tasas de supervivencia a 5 años fueron menores de 10% en pacientes con otros hallazgos en combinaciones únicas o de más de 2. Parece haber 2 subgrupos en quienes las tasas de supervivencia difieren: los pacientes potencialmente curables y los no curables. Regímenes terapéuticos correspondientes a los 2 grupos deben ser considerados.

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Invited Commentary

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Korenaga et al. attempt a differentiated approach to the problem of the extremely bad prognosis of advanced carcinoma of the stomach. They try to define subgroups which could eventually profit from an aggressive surgical procedure. The idea put

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forth by the authors is as follows: Several forms of tumor spread such as peritoneal dissemination, hepatic metastasis, widespread nodal involvement extending to tertiary or quaternary lymph nodes, and direct invasion to adjacent organs (carcinoma extending beyond the serosa and infiltrating to neighboring organs) are specified as factors influencing prognosis. The task is then to find whether subgroups that are characterized by individual factors or a combination of factors can be shown to have a favorable course by a curative surgical intervention. According to general experience, the 5-year survival time in the overall patient population is, as might be expected, bad (10.2%). The subgroups with widespread nodal