
Prognosis in the Cancer of the Stomach

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1. Introduction

Although the incidence of gastric cancer has been declining in most industrialized countries over the past two decades, it still remains the second leading cause of cancer related deaths worldwide [1]. The incidence is highest in Japan, Korea, China, Latin America and Eastern Europe. In western countries like the United States, the incidence is lower, with 21,000 new cases diagnosed each year [2]. Gastric carcinoma is one of the most frequent malignancies in the world and its clinical behavior especially depends on the metastatic potential of the tumor. In particular, lymphatic metastasis is one of the main predictors of tumor recurrence and survival, and current pathological staging systems reflect the concept that lymphatic spread is the most relevant prognostic factor in patients undergoing curative resection [3]. This is compounded by the observation that two-thirds of gastric cancer in the Western world presents at an advanced stage, with lymph node metastasis at diagnosis [4].

2. Patterns of relapse and metastasis

Gastric cancer can spread via direct extension, lymphatic and hematogenous routes and also peritoneal invasion. There are 5 ways of recurrence following surgical removal of gastric carcinoma: lymph node, remnant stomach, local, peritoneal and hematogenous recurrence. Sixty percent to 72% of gastric cancer patients succumb to recurrences within the first 2 years. Hematogenous or lymphatic spreads without intra abdominal metastases occur rarely. It may be postulated that gastric cancer prefers to spread intra abdominally, and that locoregional control is therefore an important issue in treatment strategy [5]. Locoregional recurrence rates vary from 25% to 96% depending on different detection methods and study populations. Several prognostic factors have been identified.

3. Stage

The pathologic stage has consistently been shown to be of prognostic significance for both 5-year survival and local recurrence rates [6]. The best prognosis is seen in patients with early stage of the cancer. The survival rates that come from the National Cancer Institute's SEER database and which are based on people diagnosed with stomach cancer and treated with surgery between 1991 and 2000 are as follows. (Table 1)

Stage IA	71%
Stage IB	57%
Stage IIA	45%
Stage IIB	33%
Stage IIIA	20%
Stage IIIB	14%
Stage IIIC	9%
Stage IV	4%

Table 1. Add caption

4. Histology and recurrence

Gastric cancer can recur in different pathways. The possibility of predicting the risk and type of recurrence in patients with resectable gastric cancer could have important implications for therapy, both in the surgical approach (extent of lymphadenectomy, partial or total resection) and in complementary therapies. Marelli et al. found out that the main difference was found on the onset of peritoneal recurrence in a study of 412 patients in which they compared the recurrence patterns of intestinal type and diffuse type [7]. Shiriashi et al. confirmed that most recurrences were within the first two years after surgery and rare after 5 years [8].

For intestinal type of the tumor lymph node positivity, depth of invasion, advanced age and male gender significantly increases the risk of recurrence. The patterns of relapse were mainly locoregional or hematogenous and peritoneal recurrence was limited. For diffuse type of tumors very high rates of peritoneal recurrence were observed in neoplasms with infiltration of the serosa, involvement of second level lymph nodes, and large tumor size. Locoregional recurrences were frequent in advanced forms, lymph node-positive cases, and tumors larger than 4 cm. The rate of hematogenous recurrence was generally smaller than that of peritoneal or locoregional disease. Early forms and tumors smaller than 4 cm recurred primarily via hematogenous route.

The main difference was found in the onset of peritoneal recurrence; this was observed in 34% of diffuse-type cases compared to 9% of intestinal-type cases, and was the main pathway of spread in the former. Compared to intestinal-type cells, the diffuse type showed a greater predisposition to proliferate in the peritoneum, considering that 50% of the cases with infiltration of the serosa led to peritoneal carcinomatosis, which was observed in only 16% of T3 and T4 intestinal-type cases. On the contrary, recurrences of intestinal-type tumors were mainly locoregional or hematogenous. The incidence of hematogenous recurrence did not show significant differences between the intestinal and the diffuse types; in both groups of patients, they observed a higher frequency of this recurrence in lymph node– positive cases, a finding in accord with other reports. However, the degree of involvement in the various organs was different, because the intestinal type metastasized primarily to the liver, whereas in the diffuse type the liver was involved in only half of the cases; in the other cases, hematogenous metastases involved distant organs. The data may suggest that in the diffuse type, but not in the intestinal type, superextended lymphadenectomy may play a more important role in reducing the risk of recurrence. The diffuse type may show a greater propensity than the intestinal type to metastasize to third- and fourth-level lymph nodes [7].

In a large series Nakamura et al. demonstrated that there is some correlation between the tumor histological type and the gross type. Seventy nine percent of diffusely infiltrating tumors and 69% of ulcerative infiltrating tumors were poorly differentiated and 60% of polypoid tumors were well differentiated in advanced carcinomas. In early carcinomas 89% of Type I and 77% of Type IIa lesions were well differentiated. Type IIc tumors were either well (31%), moderate (19%) or poorly differentiated (50%). In their large series of 10 thousand patients the most frequently encountered macroscopic type of advanced carcinoma was the ulcerative infiltrating tumor (41%), followed by ulcerating circumscribed type (31%). In early carcinomas type IIc (70%) was the most frequently encountered type, followed by Type II a. In advanced forms well differentiated types showed fairer prognosis [9].

Adachi et al. demonstrated that patients with poorly differentiated type show a poorer prognosis especially when the tumor is bigger than 10 cm or serosal involvement is positive. If the tumor did not invade serosa but had lymph node metastasis, survival rate was significantly lower in the well differentiated group [10]. Moriguchi et al. also demonstrated that when the tumor invasion was restricted within mucosa or submucosa the well differentiated type of tumor were associated with poorer prognosis [11]. This difference can be explained by the characteristics of well differentiated type which readily develops blood-bourne metastases irrespective of the degree of penetration by tumor cells [10].

5. Grade

The difficulty of assessing the prognosis of gastric cancer using histological methods is well known and this is also reflected in the essentially descriptive character of presently used classifications [12]. In a study by Chiaravalli et al. which they reviewed the effect of the grade on prognosis among patients with T2-T4 cancer, the more favorable behavior of grade 1

compared to grade 2 tumors and of the latter compared to grade 3 cases was confirmed. Among diffuse type cancers a low low-grade desmoplastic type with a significantly better prognosis and worse prognosis of a high-grade anaplastic subtype were identified histologically from the bulk of diffuse gastric cancers owing to their distinctive histologic, clinicopathologic, and prognostic aspects. [13]. However, the stage itself, with special reference to lymph-node metastases and invasion level beyond subserosa, remains the most important prognostic clue for gastric cancer [14].

Tumor size: In a study by Yokota et al., which they reviewed 697 patients with gastric cancer, the patients were divided into three groups: 102 patients with tumors of less than 2 cm in diameter, 392 patients with tumors of 2-7 cm in diameter, and 203 patients with tumors of more than 7 cm in diameter. Patients with larger tumors had more invasion into the gastric wall in terms of depth of invasion and more frequent lymph node metastasis than did patients with smaller tumors. Histologically, diffuse, scirrhus-type was more common in the larger tumor group. The frequency of lymphatic and vascular permeation in the larger tumor group was higher than that in the other groups. The 5-year survival rates according to tumor size were 94.3% in cases of tumors of less than 2 cm, 75.1% in cases of tumors of 2-7 cm, and 26.3% in cases of tumors of more than 7 cm. Multivariate analysis revealed that the prognosis of gastric cancer patients was affected most by depth of invasion, followed by lymph node metastasis and tumor location. Tumor size is not an independent prognostic factor. In conclusion, according to the results of univariate analysis, tumor size is clinically a predictor of survival of patients with gastric cancer. In multivariate analysis, however, it is not an independent factor, and the presence of lymph node metastasis, depth of invasion and tumor location are more important than tumor size (15). However in another study of clinicopathologic data of 479 patients who underwent curative operation for gastric carcinoma, the patients were divided into three groups: 182 with tumors measuring <4 cm (group I), 252 with tumors of 4–10 cm (group II), and 45 with tumors of 10 cm (group III). The 10-year survival rates for group I, II, and III patients were 92%, 66%, and 33%, respectively ($p < 0.01$), and the three groups were significantly different with regard to depth of invasion ($p < 0.01$), number and level of lymph node metastasis ($p < 0.01$), and stage of disease ($p < 0.01$). Multivariate analysis indicated that tumor size independently influenced the survival of patients. [16] Among patients with gastric cancer larger than 10 cm, independent prognostic factors were serosal invasion, extragastric lymph node metastasis, and liver metastasis. Prognosis after gastrectomy was determined by these tumor factors and was not associated with the patient or operation factors [17].

6. Tumor location

Middle third and distal cancers tend to decline worldwide. However, in the western populations proximal gastric cancers tend to increase even though the incidence of those cancers stays the same in Japan [18]. In a study by Saito et al, tumors of the cardia had a mean size of 6.8 cm, which was significantly larger than the mean size of 5.9 cm for tumors found in the middle- and lower third of the stomach. The incidence of serosal invasion, lymph node metastasis, and lymphatic and blood vessel invasion was higher in association with adenocarcinoma of the

cardia than with adenocarcinoma in remaining parts of the stomach. In the analysis of patients who had undergone curative resection, the 5-year survival rates were 61.6%, 79.1%, and 82.6% in patients with carcinoma of the cardia, upper one-third, and remaining middle- and lower one-third of the stomach, respectively, and the differences were statistically significant. Multivariate analysis indicated that adenocarcinoma of the gastric cardia is an independent prognostic factor. With regard to the site of recurrence, both lymph node and hematogenous recurrence were observed more frequently in the cardia than in the remaining parts of the stomach [19]. A multivariate analysis demonstrates that R0 resection is independent of other strong predictors of survival, like T, N and M [20].

7. Lymphatic and vascular invasion

Hyung et al. reviewed a total of 280 patients who underwent curative gastrectomy for advanced gastric cancer without lymph node metastasis. Lymphatic vessel invasion (LVI) was noted in 20.0%, blood vessel invasion (BVI) in 5.4%, and either LVI or BVI in 22.5%. None of the clinicopathologic features was related to LBVI. Patients with LBVI had a recurrence rate of 26.8%, whereas patients without LBVI had a recurrence rate of 13.5%. The 5-year survival rates were 82.4% for patients without LBVI and 67.1% for patients with LBVI. LBVI was shown to be an independent risk factor for recurrence [21]. Del Casar et al. reviewed 144 patients with primary gastric adenocarcinoma, who consecutively underwent surgery with a mean follow up of 33 months. LBVI was present in 46 patients (31.9%). The presence of LBVI correlated significantly with tumor stage, lymph node involvement, surgical resectability, histological type and histological grade, being present in a higher percentage among II-IV tumor stage, poorly differentiated, diffuse type, R1-R2 and lymph node-positive tumors. In addition, statistical analysis demonstrated that LBVI was significantly associated with a poorer overall patients' survival in the univariate analysis as well as in the multivariate analysis. However, their results failed to show any significant relationship between LBVI and any of the intratumoral biological parameters studies [22].

LBVI is an adverse prognostic indicator and the presence of LBVI seems to provide useful information for the prognosis and clinical management of patients with node-negative advanced and also early gastric carcinoma [23].

8. Peritoneal cytology

Mezhir et al. demonstrated that a positive peritoneal cytology, even in the absence of gross peritoneal disease, indicates a poor outcome [24, 25]. In the Dutch Gastric Cancer Group, positive cytological findings were found in 4.4% of the patients and were indicative of a poor prognosis, with a median survival of 13 months [26]. Thus, the Japanese Society for Gastric Cancer has included peritoneal cytology as part of the staging procedure, while the TNM classification system has classified cytology-positive gastric cancer patients as stage IV patients since 1997 [27,28].

9. Lymph node ratio

Xiao et al. reviewed the significance of metastatic lymph node ratio in gastric cancer and compared it to N staging of 7th edition of UICC [29]. Lymph node metastasis is one of the most important gastric cancer prognostic factors [30]. The identified number of involved lymph nodes depends on the number of lymph nodes removed and examined, which in turn depends on the surgical and pathologic procedures. Although TNM classification is a convenient and reproducible method for precise staging, it demands the examination of at least 15 lymph nodes. If the number of dissected and examined lymph nodes is small, down-migration of N stage may occur, and conversely, if the number is large, upmigration of N stage may occur, which is also referred to as stage migration in some references [31,32]. To improve prognosis prediction, the number of positive lymph nodes should be considered in the context of the number of nodes examined. The metastatic lymph node ratio (MLNR), defined as the number of positive lymph nodes divided by the number of lymph nodes retrieved, has been proposed as an alternative to classification systems that assess the absolute number of positive lymph nodes [29]. In a study by Nitti et al. the 5-year survivals according to the metastatic/examined lymph nodes ratio (N ratio) were 14%, 50%, 61%, and 82% in the group of patients with N ratio >25%, 11%-25%, 1%-10%, and 0%, respectively ($P < .0001$). At multivariate analysis, the N ratio was the best single independent prognostic factor [33]. In a study by Kulig et al., it was said that even though the LNR cannot be used as a substitute for staging with adequate lymphadenectomy, it may help to stratify patients in terms of prognosis when the number of resected lymph nodes is limited and therefore the stage is inadequately defined [34]. The metastatic lymph node ratio system reduces stage migration in patients undergoing D1 lymphadenectomy for gastric adenocarcinoma [35]. Xu et al. stated that positive N ratio classification is a better prognostic tool compared with N staging system after D2 resection in patients with gastric cancer. It can prevent stage migration and can be used regardless of the examined number of lymph nodes [36].

10. Age

In a review by Wang et al., it is stated that the prognostic value of age in gastric cancer patients remains controversial [37]. Some researchers thought that it was not an independent prognostic factor [38-40], whereas others thought that younger patients has worse prognoses than elderly due to the worse biological behaviors of tumors and histological type [41]. However, Saito et al. held that elderly patients had worse prognosis because they had limited lymph node dissection and lower tolerance of chemotherapy [42].

11. Genomics and prognosis

Gastric cancer is said to be a chronic proliferative disease with multiple genetic and epigenetic alterations [43-44]. The specific combination of alterations differs in the 2 histological types of

gastric cancer, suggesting that intestinal-type and diffuse-type carcinomas have distinct carcinogenetic pathways. Chromosomal instability (CIN); in particular, loss of heterozygosity (LOH), genomic amplifications, and DNA aneuploidy, are frequently observed in intestinal-type gastric carcinoma [45, 46]. Intestinal type of gastric cancer is thought to be generated after a multistep process of intestinal metaplasia-dysplasia-carcinoma [47]. This process of intestinal type gastric cancer development mimics the progression from adenoma to colon carcinoma, which results from the accumulation of molecular genetic alterations involving activation of oncogenes and inactivation of tumor suppressor genes [48]. Microsatellite instability and p53 mutation, reduced p27 expression, cyclin E overexpression and 6.0kb transcripts of the c-met gene are involved in malignant transformation from precancerous lesions to intestinal-type gastric cancer. In addition, DCC loss, APC mutations, 1q loss of heterozygosity (LOH), p27 loss, reduced expression of tumor growth factor (TGF) β type I receptor and HER2 gene amplification are frequently associated with an advanced stage of intestinal-type gastric carcinoma [49]. Diffuse type gastric cancer is considered to be de novo cancer, and precursor cells have not yet been identified [47]. In contrast, LOH at chromosome 17p (p53) and mutation or loss of E-cadherin are more often implicated in the development of diffuse-type gastric cancer, while loss of p27 and gene amplification of Ksam and c-met lead to disease progression and metastatic spread [49].

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