

Clinicopathological Characteristics and Surgical Treatment Analysis for Gastric Carcinoma in Stage III

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OBJECTIVE To study the clinicopathological and surgical treatment of gastric carcinoma in stage III.

METHODS A total of 484 cases of gastric carcinoma were treated with different methods and their efficacy evaluated. These included 114 and 102 cases with D2 and D3 lymphadenectomy, respectively, 48 with intraoperative radiation therapy (IORT) and 18 with peritoneal infusing chemotherapy combined with TIL.

RESULTS The total rate of lymph nodes metastasis (LNM) was 79.5% (384/484) and the degree of LNM 41.2% (4169/10121). The incidence of LNM of N1, N2, N3 and N4 was 68.8%, 34.6%, 19.6% and 3.5%, respectively. The rate of serosa linking to peripheral tissues or organs was 23.15% (112/484) including 12.5% cancerous linkage. The survival rates for patients treated with D3 lymphadenectomy at 1-, 3- 5- 8- and 10-years were significantly higher than that for D2 lymphadenectomy. The 5-year survival rate with application of IORT increased remarkably compared to the operation-alone group. Peritoneal lavage with 2000 ml of 43°C distilled water before closure of the abdominal incision and postoperative peritoneal infusing chemotherapy with TIL significantly decreased the rate of peritoneal metastasis.

CONCLUSION Due to the specificity of gastric carcinoma in stage III, the surgical principles are to perform an extensive radical operation, in combination with IORT plus different peritoneal infusing therapy to improve the long term survival rate.

KEYWORDS: gastric carcinoma, stage III, lymphadenectomy, IORT, peritoneal infusing therapy.

Gastric carcinoma (GC) is one of the most common malignant tumors of the digestive tract. Detailed pathological changes of this tumor are well known. Considering the specificity of pathological and biological features of GC in stage III,^[1-3] in this study, we explored the clinicopathological characteristics of GC in stage III in relation to our therapy used by analyzing our therapeutic results over the last 20 years. Our findings are as follows.

MATERIALS AND METHODS

General material

During the period of January, 1975 to May, 1997, 2136 patients with

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GC who had been referred to our department for surgical treatment underwent a radical operation. According to the TNM classification for GC, 832 cases were stage III, out of whom 484 patients were recruited in our study, consisting of 69 IIIa cases and 315 IIIb cases. Others were excluded because of combined angiocardopathy, endocrinopathy or lack of intact clinical data. Of the 484 cases, 445 were completely followed-up, including 315 male and 129 female (male : female = 2.5:1). The follow-up rate was up to 91.9% (considering the missed patients as died). Mean age of these 445 patients was 53.4 years (range: 25~84 years). Fifty-six cases were below 35 years. There were 285 cases (58.9%) with a long history of gastric diseases, 251 (51.7%) with epigastric pain as the main presenting symptom, 163 (33.9%) with melena or positive occult blood. Among the 457 patients who received a pre-operative barium meal examination of the digestive tract, 423 were diagnosed as GC, 61 as gastric ulcerative diseases or early GC. For 469 patients examined by gastroscopy before their operation, 451 were GC, 13 were negative and 24 suspicious benign ulcer. Among the 454 cases subjected to gastroscopy plus a barium meal examination, 431 were definitely diagnosed as GC.

Pathological data

Tumor site

Seventy-eight tumors were in the cardia, 81 in the body of the stomach, 312 in the gastric angle or artrum, with a predominance of lesser curvature of the stomach, 13 in the entire stomach.

Tumor size

Size of the tumors was in the range of 1.5~7.4 cm in diameter. Of all the 484 tumors, 235 were 1.5~3 cm; 153, 3.1~5 cm; 83, 5.1~7 cm and 13 over 7 cm.

Histological type

The numbers of well and poorly differentiated adenocarcinoma were 224 and 118, respectively. Forty-six cases were mucinous adenocarcinoma and signet ring cell carcinoma; 37 were undifferentiated

carcinoma; 7 carcinoids and 7 squamous carcinoma.

Growth pattern

There were 268 tumors that showed bolus growth, 129 nest growth and 87 diffuse growth.

The number of serosa linking to peripheral tissue or an organ

The number of serosa linking to peripheral tissue or an organ was 112 (23.6%), including 54 linking to the greater omentum, 23 to the transverse mesocolon, 24 to the pancreas and 12 to the diaphragm. Thirteen cases were cancerous linkage.

Lymph nodes metastasis (LNM)

The overall LNM rate was 79.5% (384/484) and the degree of LNM 41.2% (4169/10121). The rates of LNM of N1, N2, N3 and N4 were 68.8%, 34.6%, 19.6% and 3.5%, respectively.

Treatment

Treatment methods

A D2 lymphadenectomy was used to treat 114 patients. Greater and lesser omentums and the pancreatic capsule were removed; length of the resected duodenum was not less than 3 cm; the nearest distance from the stomach to the tumor was not less than 5 cm; lymph nodes lying at the right cardia, greater and lesser curvature of the stomach, suprapylorus and subpylorus, para-left gastric artery, and the para-hepatic artery were all resected. For carcinoma of the body, para-splenic artery nodes were also cleared. For cancer of the greater curvature, a splenic hilus lymphadenectomy was supplemented.

A D3 lymphadenectomy was used to treat 102 patients. Besides gastrectomy and lymphadenectomy similar to the above description, nodes with a high metastatic incidence lying along the N2 celiac artery, at the N3 hilus of the spleen, along the splenic artery, hepatoduodenal ligament, posterior pancreaticoduodenum, root of the mesenteric artery, middle artery of the colon and the N4 abdominal aorta were all removed. With regard to tumors of the gastric body, lymph nodes in the

left region of the cardia and total stomach were combined for excision (15 cases), with associated pancreas and spleen resection if necessary (9 cases).

IORT

A total of 48 patients with suspicious residual tumors or involved lymph nodes unable to be resected underwent IORT, including 7 cases in IIIa and 41 in IIIb. Thirty-four of the 48 patients were male and 14 female. Ages of the patients ranged from 31 to 74. There were 18 carcinomas located in gastric artrum, 12 in the body, 12 in cardia and 6 entire-stomach cancers (over 2 regions of the stomach). Various operation methods were adopted: 29 patients underwent D2 dissection; 19 underwent selective D3 dissection, 22 and 17 were subjected to distal and proximal subtotal gastrectomy, respectively and 9 cases received total gastrectomy. Intraoperative irradiation field, dose and methods were in accord with those we have described previously.^[4]

Postoperative early peritoneal infusing chemotherapy and TIL lavage treatment

After opening the abdominal cavity of GC patients in stage III, if by the naked eye there were no carcinomatous foci in the peritoneum and parietal layer, a D2 or D3 operation was carried out, plus intraoperative peritoneal lavage with 2000 ml of 43°C distilled water, peritoneal chemotherapy as follows:

15~20 days postoperative, peritoneal infusion with 1000 ml normal saline including 200 mg DDP. This was followed by abdominal cavity infusion with TIL. A total of 18 patients received the above treatment (consisting of 7 IIIa and 11 IIIb), the so-called TIL group. In addition, 83 patients with serous invasion were subjected to D2 or selective D3 resection, plus peritoneal lavage with 43°C distilled water and chemotherapy, the so-called peritoneal infusing chemotherapy group (PIC group). There were 91 cases who did not receive postoperative peritoneal infusion and chemotherapy who belonged to the so-called operation-alone (OA) group. After 2~4 years of follow-up, we compared the peritoneal implantation metastasis among the 3 groups.

RESULTS

Relationship between operation methods and survival

As shown in Table 1, the 1-, 3-, 5-, 8- and 10-year survival rates in subjects treated with D3 lymphadenectomy were significantly higher than those with D2 lymphadenectomy.

Relationship between IORT and survival

No complications were observed in the 48 patients who underwent IORT, whereas occurrence of postoperative

Table 1. Comparison of survival time between different operation methods (cases %)

Group	Cases	Surviving cases (%) at different years				
		1-	3-	5-	8-	10-
D2 lymphadenectomy	114	94(81.6)	60(52.3)	39(35.7)	33(28.3)	27(23.3)
D3 lymphadenectomy	102	94(92.1)	68(66.5)	57(56.3)	52(51.1)	49(47.5)
P value	-	<0.05	<0.01	<0.01	<0.01	<0.01

Table 2. Comparison of survival time among different operative methods plus IORT for stage III GC (%)

Group	Total cases	Cases	Survival rate with D2 operation					Survival rate with D3 operation					
			1-	2-	3-	4-	5-	Cases	1-	2-	3-	4-	5-
IORT	48	9	100	100	87.5	75	60	39	100	100	93.1	85.5	61
OA	216	114	81.6	70.4	52.3	43.3	35.7	102	92.1	85	66.5	62.2	56.3
P value	-	-	<0.05	<0.001	<0.001	<0.001	-	<0.005	>0.50	>0.10	<0.001	<0.005	>0.05

exsufflation was delayed about 24 h in these subjects as compared to those not receiving IORT. For GC patients in stage III, the 1-, 2-, 3-, 4- and 5-year survival rates were 89.4% , 81.4% , 71.7% , 65.1% , 60.0% , respectively. Compared with 380 cases who received a simple operation during the period of 1975~1989, the 5-year survival rate had increased by 14.6% (60% vs 45.4% , $P<0.005$). One-year through 5-year survival rates in GC patients in stage III treated with D2 surgery plus IORT were significantly higher than those treated by an operation alone ($P<0.05$). For patients receiving D3 plus IORT, 1-year through 5-year survival rates were slightly higher than those treated only by an operation, with a significant difference in the 3- and 4-year survival rates but not in the 5-year survival rate (Table 2).

Relationship between postoperative peritoneal infusing chemotherapy and incidence of peritoneal metastasis

After 2~4 years of follow-up, we found that the rates of peritoneal implantation metastasis in the TIL, PIC and operation-alone group were 3.7% (1/27), 12.0% (10/83) and 31.9% (29/91). The differences among the 3 groups were significant ($P<0.05\sim 0.005$).

DISCUSSION

Since most of the GC in stage have the presence of a serous invasion and regional LNM, as well as existence of exfoliated carcinoma cells in the abdominal cavity and even in the vessels, active treatment for over half of GC patients in stage III has ended in failure. The main reason relates to the pathological characteristics of GC stage III, such as indefinite nodal involvement, peritoneal implantation, minute metastasis and tumor residue. With respect to the various above factors, the following results were acquired through analysis of the therapeutic results in our hospital over the last 20 years.

Extent of gastrectomy and clearance of lymph nodes

In the present study, high LNM rates of N2 and N3 were observed in GC patients in stage III, 34.6% and 19.6%

respectively, which is in agreement with other related reports.^[5,6] Therefore, for localized GC, tissues away from the tumor margin by 3~4 cm should be resected and for infiltrating GC by 5~6 cm. D2 and D3 surgery were primarily adopted under these circumstances. Para-aortic lymphadenectomy was conducted given suspicious existence of N0 LNM. For GC, once the serous layer was invaded, the rate of nodal involvement remarkably elevated. We had explored the tendency of LNM for 1200 GC patients, and discovered that the rates of LNM with an absence or presence of serous invasion were 50.0% and 89.2% , respectively, which indicated it is not sufficient to clear N1 and N2 nodes for stage III GC. That is, for carcinomas of the artrum, subtotal gastrectomy was supplemented by N3 lymphadenectomy at the hepatoduodenal ligament area, posterior pancreaticoduodenal nodes, para-middle artery nodes of the colon and root of the mesenteric artery nodes. Nodal metastasis in the left cardia should also be resected, plus total gastrectomy. For cancers of the stomach body, hepatoduodenal lymph nodes should be cleared; if LNM were discovered in the posterior pancreaticoduodenal nodes, root of the mesenteric artery nodes, and para-middle artery nodes of the colon, the corresponding lymph nodes should be removed; the surgical principle of total gastrectomy remains. While for a non-infiltrative tumor, with the upper margin away from the cardia by 7 cm, a subtotal gastrectomy, preserving the fundus of the stomach can be adopted. A favorable therapeutic effect can be achieved with complete clearance of the carcinomatous foci and reasonable lymph node dissection.

In the current study, the 1-, 3-, 5-, 8- and 10-year survival rates for 102 patients subjected to D3 resection were all higher than those receiving a D2 operation, which shows that residual nodes with carcinomatous cell metastasis may exist with D1 or D2 surgery. Therefore a D3 or wider extent lymphadenectomy should be advocated for GC patients in stage III to guarantee completeness of the radical gastrectomy, and thus, to improve long-term survival of GC patients.

IORT

IORT can serve as an effective supplement to surgical

treatment, being of great value to control minute focal spread and metastasis. Application of IORT is effective because the tumor and its peripheral tissues are directly irradiated during IORT, with a definite irradiation area, while the normal tissue is little influenced. For GC patients in stage III, incomplete therapy always results in the tumor moving to peripheral tissues or organs and tumor invasion. In our study, the rate of serosa linking to peripheral tissues or organs was 23.2% (112/484) and the rate of cancerous linkage was 12.5% (13/112). Under imperfect radical treatment residual tumor will be present, so it is necessary to use IORT.

As for the therapeutic effect of IORT, Abe et al.^[7] compared patients who were treated with an operation plus IORT versus those receiving an operation alone. The survivals of 115 patients in stage II through IV who received IORT increased by nearly 10~20% at 5 years. When serosal invasion or N2 and N3 LNM were observed, the 5-year survival rate for patients who underwent IORT increased by 10%. Ogata et al.^[8] compared survivals between 58 patients who were subjected to a radical operation plus IORT (group 1) versus controls who only received radical surgery (group 2). They found no significant difference in the 5-year survival rate for stage IV GC patients between the 2 groups; of the stage II GC patients, all 11 patients of group 1 were alive, whereas in group 2, the 4- and 8-year survival rates were 60% and 48%, respectively; in stage III patients, the 8-year survival rate of group 1 was 55% vs 35% in group 2. In that study, cases belonging to stage I and IV did not benefit from an operation plus IORT, while the 5-year survival rate for those in stage II and III subjected to tumor resection plus IORT increased by 14.4%~20.0% as compared to those subjected to a simple resection; 1-year through 5-year survival rates for patients in stage III who underwent D2 dissection plus IORT were enhanced by 24.3% compared with a simple D2 dissection; 1-year and 4-year survival rates for those receiving a D3 dissection plus IORT were significantly different from those with a D3 resection alone, while the 5-year survival rate merely increased by 4.7%. These results indicate that IORT could improve survival of stage III GC patients.

According to our long-term clinical experience, we might come to the conclusion that IORT should be utilized under the following situations: 1) suspicious residual tumor presence, but lack of macroscopic metastasis of lymph nodes and connective tissues; 2) minority LNM under macroscopic observation; 3) macroscopically, a great deal of LNM or tumor invasion into the connective tissue; 4) obvious residual carcinoma which we are unable to remove.

Intraoperative peritoneal infusion and postoperative early peritoneal chemotherapy

It has been reported that for GC patients the rate of peritoneal metastasis reached 40%~50% and that the 3-year survival rate was as low as 15.6% once the serous layer was invaded.^[9,10] Therefore, it is necessary to adopt intraoperative peritoneal infusion and postoperative early peritoneal chemotherapy for GC stage III patients to decrease the peritoneal implantation and thus, to improve the 5-year postoperative survival rate. For patients in GC stage III, we have tried to carry out intraoperative infusion with a 43°C hypo-osmolar solution plus postoperative early peritoneal-infusing chemotherapy using 200 mg cisplatin dissolved in normal saline. However peritoneal metastases were found in 17.7% cases. In recent years, based on the above treatments, peritoneal infusion with TIL was carried out before closing the abdomen to prevent peritoneal implantation. After 2~4 years of follow up, our patients obtained a peritoneal metastasis rate of 3.7%, which was significantly lower than the PIC group rate of 18.7%, and operation-alone group of 31.9%. The results suggest that the drug combination can reduce peritoneal implantation.

For GC patients in stage III, due to their specificity of clinicopathological characteristics, multiple measures should be taken, such as an extensive radical operation in combination with IORT to deal with residual tumor, postoperative early peritoneal infusing chemotherapy with TIL etc, to improve the long-term survival rates for patients with GC in stage III.

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