

Study on the risk factors of lymphatic metastasis and the indications of less in vasive operations in early gastric cancer

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INTRODUCTION

The principle of surgical treatment for gastric cancer is the radical resection although the suitable resecting range for different cases of gastric cancer is still being argued upon^[1-9]. However, the diagnostic accuracy of early gastric cancer (EGC) without lymphatic metastasis has obviously improved with an improvement in the diagnostic technique and due to the accumulation of knowledge on the biological profiles of EGC^[10-17]. The D₂ lymph node excision was used as a regular operation to treat the EGC previously. But the concept for the EGC without lymphatic metastasis has gradually changed and the less invasive resections has been applied in some cases^[18-20]. This study aimed at investigating the risk factors of lymphatic metastasis in EGC in order to find out the proofs for the suitable indications for less invasive operations such as endoscopic mucosal resectioning (EMR), laparoscopic and laparotomic resectioning.

MATERIALS AND METHODS

From 1978 to 1999, 520 cases of EGC with operative and pathological analyses were studied. Among them, 287 were male and 233 female, with an average age of 62 years (32-81). The samples from the primary tumor and the

metastatic lymph nodes were collected and examined as previous reports distinguishing the tumor was limited in mucosal layer (m Ca) or submucosal layer (sm Ca) of stomach^[10] were scanty. According to the gross differences of the following groups were constituted of II_c+III, II_c, II_b, II_a and I.

Sixty-six cases diagnosed by the ultrasound endoscopic examination received the less invasive operative technique. This resection retained the partial omentum and resected the 1st station and No 7 of lymph nodes. In this operation, the dissection was made and the omentum was cut off in (3-4) cm places away from or along the blood vessels in greater and less curvature of the stomach. And the No 7 lymph nodes were resected and blocked or picked out. Hepatic branch of vagus had better to be protected possibly. Mouth margin and anal margin for gastrectomy was over 2 cm away from the tumor site. All of 259 cases received radical resectioning of N₂ lymph nodes or a more radical resection.

The rate of lymphatic metastasis and the morbidity of intestinal obstruction after operation and the expression of long-term survival were statistically analyzed by Check test or by log-rank test respectively. *P* value less than 0.05 was considered statistically significant.

RESULTS

In this study, the risk factors regarding the occurrence of lymphatic metastasis were investigated. The long-term survival analysis and the complications relating to the less invasive operation were studied at the same time.

Gross type

Lymphatic metastasis happened the most easily in II_c+III subgroups of both m Ca and sm Ca, and secondly in II_c subgroups. In II_c+III subgroups, the lymphatic metastasis could be identified in 2 cases of m Ca and 20 cases of sm Ca, and one n₂ lymphatic metastasis was observed in m Ca and 10 in sm Ca (Table 1). No n₂ lymphatic metastasis could be found in other subgroups of m Ca. However, this n₂ lymphatic metastasis could be observed in sm Ca in all groups except II_b.

Invading depth

Forty-four cases of n₁ lymphatic metastasis and 14 cases of n₂ lymphatic metastasis (58 cases of lymphatic metastasis in

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total, 11.2%) could be demonstrated in all cases of EGC. Four (1.5%) of 275 cases suffering from the m Ca had lymphatic metastasis, of which one case shared n_2 lymphatic metastasis (Table 2). Lymphatic metastasis was identified in 54 (22.0%) out of 245 cases in sm Ca group, of which 13 cases were of n_2 lymphatic metastasis. This result showed that lymphatic metastasis was more frequent in sm Ca than in m Ca ($P < 0.05$).

Table 1 Lymphatic metastasis relating to gross types (%)

Gross types	m Ca (n = 275)	sm Ca (n = 245)
II _c +III	2.5 (2/85) ^{a,b}	25.3 (20/79)
II _c	1.7 (2/120) ^b	20.2 (17/84)
II _b	0 (0/3)	0 (0/4)
II _a +II _c	0 (0/29)	23.8 (10/42)
II _a	0 (0/34)	25.0 (2/8)
I	0 (0/4)	17.9 (5/28)

^aNumber of positive lymph nodes/total numbers of cases.

^b $P < 0.01$, vs each subgroup of II_b, II_a+II_c, II_a or I types.

Table 2 Lymphatic metastasis relate(LMR) of m and sm Ca (%)

Invading depth	n_1 LMR	n_2 LMR	Total LMR
m Ca (n = 275)	1.1 (3) [*]	0.4 (1)	1.5 (4) ^b
sm Ca (n = 245)	16.7 (41)	5.3 (13)	22.0 (54)
Total cases (n = 520)	8.5 (44)	2.7 (14)	11.2 (58)

^{*}Number of cases. ^b $P < 0.01$, vs sm Ca.

Tumor size with or without ulcer

With tumor size less than 20 mm in m Ca, there was no lymphatic metastasis in 122 of 275 cases regardless whether accompanied with ulcer or not. In 153 cases with tumor larger than 20 mm, there were 4 cases of lymphatic metastasis in m Ca ($P < 0.01$, Table 3). Among 164 cases with m Ca and without ulcer, the lymphatic metastasis could be observed only in one with 25 mm of tumor. On the other hand, 3 of 111 cases of lymphatic metastasis could be found in ulcer group, in which all tumors were larger than 30 mm. These findings indicated that lymphatic metastasis was more significantly in cases with tumor size larger than 20 mm subgroups, especially those with ulcer ($P < 0.05$).

Table 3 Lymphatic metastasis related to tumor size with or without ulcer (%)

Ulcer diameter- (cm)	m Ca (n = 275)		sm Ca (n = 245)	
	With ulcer (n = 111)	Without ulcer (n = 164)	With ulcer (n = 110)	Without ulcer (n = 135)
≤ 2	0 (0/43)	0 (0/79)	16.7 (3/18)	3.1 (1/32)
~ 3	0 (0/21)	2.4 (1/42)	20.8 (5/24)	21.1 (8/38)
~ 4	5.3 (1/19)	0 (0/15)	20.0 (4/20)	24.0 (6/25)
~ 5	6.7 (1/15)	0 (0/14)	18.8 (3/16)	18.2 (4/22)
≥ 6	1 (1/13)	0 (0/14)	43.8 (14/32)	33.3 (6/18)
Total No	2.7 (3/111) ^a	0.6 (1/164)	26.4 (29/110) ^a	18.5 (25/135)

^a $P < 0.05$, vs ulcer subgroup in each group.

In sm Ca, 4 out of 50 (8.0%) cases of lymphatic metastasis could be identified in cases with tumor size less

than 20 mm with or without ulcer, which showed that the radical resection with standard lymph node excision could be carried out even in small tumor sized sm Ca.

In 135 cases of sm Ca without ulcer, 25 (8.5%) cases were demonstrated to have lymphatic metastasis, out of which 12 (11.3%) cases belonged to n_2 lymphatic metastasis. But 29 out of 110 (26.4%) cases of sm Ca with lymphatic metastasis were proven to occur in the ulcer subgroup, in which 7 (6.4%, $P < 0.05$) cases had n_2 lymphatic metastasis. Therefore, the n_2 lymphatic metastasis happened more significantly in sm Ca than in m Ca.

Pathological classification

One hundred and forty-three out of 275 cases (52.0%) with m Ca had well-differentiated adenocarcinoma in which there was no lymphatic metastasis. Two out of 58 cases (3.4%) and 2 out of 57 cases (3.5%) sharing lymphatic metastasis were respectively identified in the poorly-differentiated group and the non-differentiated group of EGC. Fifty-four out of 245 (22.0%) cases with lymphatic metastasis were observed in sm Ca, out of which there were 21 (8.6%), 11 (4.5%), 15 (6.1%), and 7 (2.9%) cases respectively in each group of well-differentiated, poorly-differentiated, non-differentiated and ringed cells cancer. Difference in pathological classification could not significantly result in the increase of lymphatic metastasis, but n_2 lymphatic metastasis was more easily recognized in worst differentiated groups.

Comparison of D₂ and D₁₊₇

resections In a study regarding the less invasive D₁₊₇ resection, this resection and D₂ or more radical lymph node excision were separately carried out in 66 cases and 259 cases during 1988-1999. All cases resulted in the curable resection and the longest follow-up was of 10 years. In D₁₊₇ group, only one case was histopathologically demonstrated for the occurrence of lymphatic metastasis. Twelve cases diagnosed as m Ca preoperatively were sm Ca and others were m Ca. In investigating the postoperative complications, 1 out of 66 cases (1.5%) with D₁₊₇ resection and 39 out of 259 cases (15.1%) with D₂ resection suffered from the intestinal obstruction ($P < 0.01$). But no mortality occurred in D₁₊₇ resection group and 2 cases (0.8%) died within one month after D₂ operation.

The investigation of long-term survival showed that the survival rates of 1 and 5 years in D₁₊₇ and D₂ operation groups were respectively 98.3% vs 97.6% and 90.2% vs 92.1%, in which no significant differences could be observed.

DISCUSSION

As is well known, the degree and the range of lymphatic metastasis is dependant on the biological features of the primary tumor^[10,12-14]. This study showed that one of the main risk factors for the lymphatic metastasis was the tumor invading depth infiltrating through the mucosal layer and

the tumor size being larger than 20 mm. In sm Ca with tumor size larger than 20 mm, the morbidity of n_2 lymphatic metastasis happened with an increase in the tumor size. Therefore, correct determination of the invading depth and the tumor size are key points for the less invasive surgeries in EGC. The indications for endoscopical mucosal resection (EMR)^[20-21], laparoscopic resection^[22-31] and less invasive resection by laparotomy^[20,32-33] should be limited in the cases of EGC without lymphatic metastasis. Even for less invasive resection by laparotomy, it should be indicated only for n_1 lymphatic metastasis without ulcer, I, II_a and II_b gross types as II_c types with tumor size less than 20 mm although such indications have not been accepted ubiquitously^[10,20,32-33]. The less invasive surgery by laparotomy has become one of the main choices in surgical treatment of EGC currently. The range of less invasive operation includes the partial gastrectomy and regional lymph node excision as well as the retains of the omentum, vagus, pylorus and so on^[10,14,27]. The less invasive operations for m Ca or sm Ca have been proven to share the good results of long-term survival^[14,33], and at the same time, less invasive surgery is required.

Development of less invasive operations by laparotomy have made both MER and laparoscopic resection applicable in the treatment of EGC^[18-32]. The rate of complete resection for primary tumors and metastatic lymph nodes by EMR or laparoscopic resection was between 45%-85%. This resection rate was lower because most tumors were larger than 10 mm and some were located in the cardia, lesser curvature of gastric body as well as latter wall of stomach^[9,11,14]. Mucosal resectioning by laparoscopic surgery including lesion lefting resection^[31] and gastric mucosal resection^[20,23] comes in between EMR and less invasive laparotomy. Advantages of this laparoscopic surgery are to get more satisfactory resectioning of the entire layer of the gastric wall at the lesion site and the regional lymph nodes of n_1 around the tumor in comparison to EMR^[20,29-31]. If the tumor infiltrated to the sm Ca or the vessels in the gastric wall, the radical resectioning at the 2nd station of lymph nodes should be carried out as the first choice^[1,9,32,34].

Judgements for the invading depth of EGC before operation are mainly based on the gastric fiber examination with the ultrasound. On the application of the ultra sound endoscopy, especially at 20 MHz, correct diagnostic has been observed in over 80% cases and identification of m Ca or sm Ca was easier^[15-17,34]. At the same time, n_2 lymphatic metastasis happened more easily in sm Ca. Therefore, D₂ lymph node excision should be applied in sm Ca if the diagnosis is doubtful before or during operation. The investigations on the metastasis and the regional invasion of gastric cancer has the support of not only clinicopathological studies but the genetic and molecular biological studies also^[35-42]. At present, a very careful choice should be made for the less invasive operations,

especially for EMR and laparoscopic surgery, as making a correct judgement for the invading depth of tumor in stomach before operation^[16-17,34] is very difficult.

REFERENCES

- Noguchi Y, Imada T, Matsumoto A, Coit DG, Brennan MF. Radical surgery for gastric cancer-A review of the Japanese experience. *Cancer*, 1989;64:2053-2062
- Li GF, Xie SB, Sun H, Yang XH, Liu WJ, Zhai Q, Zhou YX, Li ZH, Zhang GM. An investigation of intra-arterial chemotherapy infusion and embolization combined with abdominal chemotherapy for advanced gastric cancer. *World J Gastroenterol*, 1998;4:71-74
- Torii A, Sakai M, Inoue K, Yamabe H, Ueda S, Okuma M. A clinicopathological analysis of early gastric cancer: retrospective study with special reference to lymph node metastasis. *Cancer Detect Prev*, 1994;18:437-441
- Jiang BJ, Gao YF, Sun RX, Sun H, Lu M, Tu CL. Clinical study on the dissection of lymph nodes around abdominal aortic artery in advanced gastric cancer. *Zhongguo Putong Waikexue Zazhi* (in press)
- Yonemura Y, Katayama K, Kamata T, Fushida S, Segawa M, Ooyama S, Miwa K, Miyazaki I. Surgical treatment of advanced gastric cancer with metastasis in para aortic lymph node. *Int Surg*, 1991;76:222-225
- Uyama I, Ogiwara H, Takahara T, Kikuchi K, Iida S, Kubota T, Kunai K, Kitajima M. Spleen and pancreas-preserving total gastrectomy with superextended lymphadenectomy including dissection of the para aortic lymph nodes for gastric cancer. *J Surg Oncology*, 1996;63:268-270
- Okamura T, Tsujitani S, Korenaga D, Haraguchi M, Baba H, Hiramoto Y, Sugimachi K. Lymphadenectomy for cure in patients with early gastric cancer and lymph node metastasis. *Am J Surg*, 1988;155:476-480
- Boku T, Nakane Y, Okusa T, Hirozane N, Imabayashi N, Hioki K. Strategy for lymphadenectomy of gastric cancer. *Surgery*, 1989;105:585-592
- Nakamura K, Morisaki T, Sugitani A, Ogawa T, Uchiyama A, Kinukawa N, Tanaka M. An early gastric carcinoma treatment strategy based on analysis of lymph node metastasis. *Cancer*, 1999;85:1500-1505
- Lin H, Jiang BJ, Wu T. Influencing factors on the lymph metastasis and less invasive operations in early gastric cancer. *Zhongguo Putong Waikexue Zazhi*, 1999;8:253-255
- Sano T, Kobori O, Muto T. Lymph node metastasis from early gastric cancer: endoscopic resection of tumor. *Br J Surg*, 1992;79:241-244
- Yamao T, Shirao K, Ono K, Kondo H, Saito D, Yamaguchi H, Sasako M, Sano T, Ochiai A, Yoshida S. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer*, 1996;77:602-606
- Zhang XY. Some recent works on diagnosis and treatment of gastric cancer. *World J Gastroenterol*, 1999;5:1-3
- Sakuramoto S, Hiki Y, Shimao H, Sakakibara Y, Kakita A, Kida M. Option of treatment for early gastric cancer with regard to lymph node metastasis. *Digestive Surg*, 1997;20:679-689
- Lin H, Jiang BJ, Gao YF, Zhang MD, Tu CL. Application of needle type of laparoscope in the evaluation on the end stage of digestive cancer. *Zhongguo Meitan Gongye Yixue Zazhi*, 2000;3:81-82
- Niwa Y, Goto H, Arisawa T, Kameyama H, Matsui M, Nomura N, Hosoi T, Hatakeyama T. Endoscopic ultrasonography in the diagnosis of the depth invasion of gastric cancer. *Digestive Surg*, 1997;20:691-697
- Adachi Y, Inomata M, Kitano S. New criteria for early gastric cancer. *Oncol Rep*, 1997;4:1235-1241
- Tsujitani S, Kaibara N. Less invasive treatment for early gastric cancer with special reference to prognosis and quality of life of patients. *Digestive Surg*, 1997;20:669-677
- Yoshino K, Ogawa S. Modified surgery for gastric cancer in early stage. *Digestive Surg*, 1997;20:715-723
- Wu T, Jiang BJ, Tu CL. Endoscopic Surgery in early gastric cancer. *Zhonghua Xiaohua Neijing Zazhi*, 1998;15:123-125
- Yamashita Y, Maekawa T, Shirakusa T. Endoscopic surgery assisted open gastrectomy with less incision in early gastric cancer. *Operation*, 1995;49:1301-1306
- Ohgami M, Ohtani Y, Igarashi N, Fujita K, Ishikawa H, Kubota T, Kumai K, Kitajima M. Laparoscopic surgery for mucosal gastric cancer. *Digestive Surg*, 1997;20:705-713
- Sakuramachi S, Kimura T, Kobayashi T. Laparoscopic surgery for early

- gas tricccancer: Intra-luminal surgery using fine instruments. *Digestive Surg*, 1997;20:1453-1459
- 24 Munakata Y, Hayashi K. Laparoscopy assisted antral gastrectomy. *Digestive Surg*, 1997;20:1461-1468
- 25 Matsumoto S, Kawabe N, Suzuki K, Morishima T. Local excision of the early gastric cancer with lesion lifting method: From extraluminal approach to endoluminal approach. *Digestive Surg*, 1997;20:1469-1475
- 26 Ohashi S, Oriyama T, Kanno H, Akashi A, Sasaoka H, Nishino M, Sakamaki Y, Son K. Laparoscopic intra gastric surgery for early gastric cancer. *Digestive Surg*, 1997;20:1477-1482
- 27 Tanimura H, Nakai Y, Takifuji K. Laparoscopic D1+ α dissection of the perigastric lymph nodes for early cancer in the antrum or lower body of the stomach. *Digestive Surg*, 1997;20:1483-1490
- 28 Shiraishi N, Adachi Y, Kitano S. Laparoscopy assisted distal gastrectomy for early gastric cancer. *Digestive Surg*, 1997;20:1513-1518
- 29 Yasutake T, Ayabe H, Miura T. Laparoscopic partial gastrectomy for early gastric cancer. *Digestive Surg*, 1997;20:1507-1511
- 30 Ohgami M, Ishibiki K, Kitajima M. Partial resection by laparoscopy for early gastric cancer. *Operation*, 1993;47:587-597
- 31 Matsumoto S, Kawabe N, Kawabe J. Application of lesion lifting for partial gastrectomy in early gastric cancer. *Operation*, 1995;49:1307-1312
- 32 Lu M, Wu T, Jiang BJ. Less invasive resection by laparotomy in early gastric cancer without ulcer. *Fubei Waike*, 1999;12:189-190
- 33 Inoue K, Tobe T, Kan N. Problems in the definition and treatment of early gastric cancer. *Br J Surg*, 1991;78:818-822
- 34 Abe S, Yoshimura H, Nagaoka S. Long term results of operation for carcinoma of the stomach in T1/T2 stage: critical evaluation of the concept of early carcinoma of the stomach. *J Am Coll Surg*, 1995;181:389-394
- 35 Zhao WM, Ma XH, Li ZJ, Yang CF. The effect of nitric oxide on gastric carcinoma metastasis. *World J Gastroentero*, 1998;4(Suppl 2):78-81
- 36 Dai J, Yu SX, Qi XL, Bo AH, Xu YL, Guo ZY. Expression of bcl-2 and c-myc protein in gastric carcinoma and precancerous lesions. *World J Gastroentero*, 1998;4(Suppl 2):84-87
- 37 Zhan WH, Ma JP, Peng JS, Gao JS, Cai SR, Wang JP, Zheng ZQ, Wang L. Telomerase activity in gastric cancer and its clinical implications. *World J Gastroentero*, 1999;5:316-319
- 38 Zhao DC, Lu YZ, An W, Shi H, Zhao ZM. Poorly differentiated gastric neoplasms immunohistochemical analysis and significance. *World J Gastroentero*, 1998;4(Suppl 2):102-104
- 39 Zhang L, Fu HM, Jin SZ, Zhou CG. The relation between p16 expression and biological behavior of gastric carcinoma. *World J Gastroentero*, 1998;4(Suppl2):109-111
- 40 Gu HP, Shang PZ, Hu HX, Li ZG, Li CG. Relationship between cell adhesion molecule CD15 and proliferating cell nuclear antigen (PCNA) expression in gastric cancer and precancerous lesions. *World J Gastroentero*, 1998;4(Suppl 2):60
- 41 Yakoob J, Hu GL, Fan XG, Zhang Z. Telomere, telomerase and digestive cancer. *World J Gastroentero*, 1999;5:334-337
- 42 Zhao WM, Ma XH, Li ZJ, Yang CF. The effect of nitric oxide on gastric carcinoma metastasis. *World J Gastroentero*, 1998;4(Suppl 2):78-81

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