Review

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Surgical strategy for early gastric cancer

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The diagnostic and therapeutic options in early gastric cancer are reviewed. In Japan, the rate of detection of early gastric cancers has increased so that minute gastric cancers can now be identified as a result of advances in diagnostic methods. The results of histopathological staging of a large number of resected specimens have led to three surgical options based on size and depth of the primary lesion, namely classical R_2 resection, radical resection with limited lymphadenectomy and endoscopic surgery.

Keywords: Early gastric cancer, lymph node metastasis, radical operation with limited lymphadenectomy, endoscopic surgery

The prognosis in gastric cancer has improved markedly in Japan during the last three decades. The most important reason is that the rate of early detection has increased owing to improved radiography and endoscopy. Recent figures show that in most Japanese hospitals 30–40 per cent of all gastric malignancies are detected at an early stage[1–4]. The other reason for improved prognosis is based on better staging following the general rules for the Gastric Cancer Study in Surgery and Pathology established by the Japanese Research Society in 1962. This has provided a large database resulting in a greater understanding of the lymphatic spread of early gastric cancer and allowing a more rational approach to lymphadenectomy[5,6]

The prognosis after curative gastrectomy for early gastric cancer is very favourable, the 5- and 10-year survival rates being over 90 per cent and 80 per cent respectively in Japan[1,2,6–13]. When early gastric cancers are divided into mucosal and submucosal cancers, the prognosis for mucosal cancers is much better. The Japanese definitions and macroscopic classification of early gastric cancer are widely used in Western countries. In Europe and North America 5-year survival rates are also over 90 per cent, even though the numbers are small[14–22]. Thus, the favourable prognosis of early gastric cancer holds world-wide and emphasizes the importance of early detection of cancers. While the rate of lymph node metastasis for mucosal cancers is low (about 3 per cent), that for submucosal cancers is about 20 per cent. Metastasis to sites other than lymph nodes is very rare in patients with early gastric cancer, so that lymph node dissection in combination with complete resection of the lesion results in cure for most patients. For this reason lymphadenectomy can be modified, unlike the situation in advanced gastric cancer where the R_2 operation (complete dissection of the group 2 lymph nodes) has been the standard operation in Japan for over three decades. In early gastric cancer the rate of lymph node metastasis depends not only on the depth of the primary lesion but also on sex, age, histological type and tumour morphology.

This paper reviews the diagnostic and therapeutic methods that are currently used in Japan and Western countries, and attempts to define optimum therapy.

Our clinicopathological data were evaluated on the basis of the general rules for the Gastric Cancer Study in Surgery and Pathology[23] where the regional lymph nodes are numbered according to their anatomical location (*Table 1*). They were also classified into groups 1, 2 and 3 according to the location of cancer in the stomach. Gastric resection based on lymph node clearance was classified as follows: R_0, gastric resection including the incomplete removal of group 1 lymph nodes; R_1, gastric resection including the complete removal of group 1 lymph nodes alone; R_2, gastric resection including the complete removal of groups 1 and 2 lymph nodes; and R_3, gastric resection including the complete removal of groups 1, 2 and 3 lymph nodes. Histopathologically, papillary adenocarcinoma and tubular adenocarcinoma were grouped together as differentiated, whereas poorly differentiated adenocarcinoma and signet-ring cell carcinomas were regarded as undifferentiated adenocarcinoma. Macroscopic or descriptive classification of early gastric cancer follows that of the Japanese Society for Gastroenterological Endoscopy[24] (*Figure 1*).

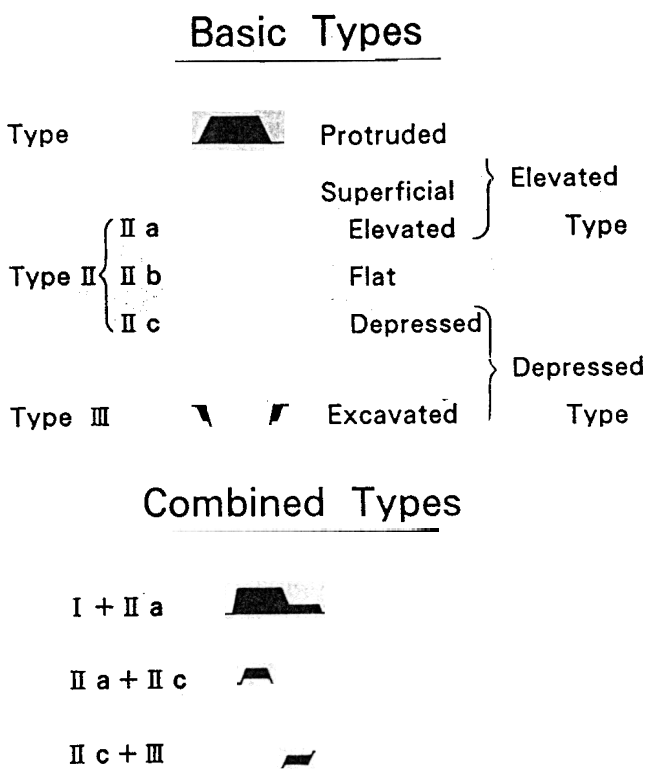
Diagnosis of early gastric cancer

An accurate preoperative diagnosis is essential. The first step is to determine whether the cancer is early or advanced. Early gastric cancers should be subdivided according to (1) whether the malignancy is confined to the mucosa or has invaded the submucosa; (2) its macroscopic appearance; (3) whether it is multifocal; and (4) its histological type[25–28]. Assessment is made by radiography and endoscopy. In Western countries endoscopy is generally regarded as more sensitive than radiography[7–20,29,30], hence endoscopy is the diagnostic method of first choice. With endoscopy, the rate of detection of early gastric cancers has increased to about 15 per cent[15–17,20,31]. On the other hand, some Japanese reports indicate that with improved photographic methods and double contrast radiography, there is no difference in the diagnostic accuracy of the two techniques[32,33].

Table 1 *Grouping and lymph node designation used in the Cancer Study*

Group	Location of cancer		
	Lower third	Middle third	Upper third
(N_1)	3, 4, 5, 6	3, 4, 5, 6	1, 2, 3, 4
(N_2)	1, 7, 8, 9	7, 8, 9, [illegible], 11	5, 6, 7, 8, 9, 10, 11
3 (N[illegible]	10, 11, 12 [illegible], 14	[illegible], 13, 14	12, 13, 14, 110, 111

Regional lymph nodes of the stomach: 1, right paracardial; 2, left paracardial; 3, lesser curvature; 4, greater curvature; 5, suprapyloric; 6, infrapyloric; 7, left gastric artery; 8, common hepatic artery; 9, coeliac artery; 10, splenic hilus; 11, splenic artery; 12, hepatic pedicle; 13, retropancreatic; 14, mesenteric root; 110, lower thoracic paraoesophageal; 111, diaphragmatic



Figure

Even though endoscopy is observer-dependent, newer developments have made this approach more informative. These advances include dye spraying methods[34,35], magnified endoscopy[36,37], electronic endoscopy[38–41] and endoscopic ultrasonography[42–44]. These improvements in diagnostic techniques have been associated with an increase in the numbers of mucosal, depressed and small (less than 2 cm diameter) cancers among early gastric cancers[4,6].

While early gastric cancer can be differentiated from advanced gastric cancer in 80–90 per cent of cases[45–47], the preoperative differentiation between mucosal and submucosal cancers is often not achieved even with endoscopic endoluminal ultrasound. The accuracy in elevated lesions (I and IIa) is high[45–48] but the preoperative diagnosis of depressed lesions (IIc and III), especially those associated with ulceration, is poor[46–49]. Despite a high reputation for determining the depth of invasion, endoluminal ultrasound is accurate in only 70–80 per cent of of cases of ulcerating early gastric cancer because of the degree of fibrosis in the submucosa and muscular propria[43,44,50,51]. Furthermore, current endoluminal ultrasound probes require that the patient drinks a considerable volume of degassed water, endoscopic visualization is often suboptimal because the optics on the endoscopes are poor, and the endoscopes themselves have a wide diameter making patient co-operation poor. Further improvements in the development and design of these devices is needed before their full benefit can be realized.

Preoperative diagnosis of metastatic lymph nodes

The preoperative diagnosis of lymph node metastasis used to rely on examination such as computed tomography (CT)[52–55] and ultrasonography[56]. These techniques visualize only enlarged lymph nodes but do not differentiate hyperplasia from neoplasia. In early gastric cancer lymphatic metastases are largely confined to the perigastric lymph nodes which are usually small. Attempts to improve the accuracy of preoperative lymph node involvement include immunolocalization with an isotope, endoscopic lymphography[57], endoluminal ultrasound[44,58] and dynamic CT[52]. In endoscopic lymphography[57] contrast medium is injected into the submucosa or muscle layer near the tumour at endoscopy followed by plain radiographic examination. Non-metastatic lymph nodes are usually less than 5 mm in size and have a finely nodular appearance. Metastatic lymph nodes are usually visualized as filling defects, diffuse lymphatic swellings, areas of uptake with marginal irregularity and other abnormalities.

Endoscopic ultrasonography may incorporate a 10 per cent oil-in-water emulsion administered orally[58]. This technique allows visualization of the perigastric lymph nodes 2–3 h later. The ultrasonographic visualization rate of lymph nodes surrounding the gastric wall was 69 per cent for nodes over 3 mm in diameter and 76 per cent in nodes exceeding 5 mm in diameter. Uninvolved lymph nodes were characterized by echo enhancement at their margin and inside the node after the administration of the emulsion. By contrast, metastatic lymph nodes showed no enhancement in spite of administration of the emulsion. The accuracy of diagnosis of lymph node metastasis by endoluminal ultrasound after administration of the emulsion had a sensitivity of 92 per cent and specificity of 100 per cent in lymph nodes over 3 mm diameter.

While there are many reports[59,60] on the use of dynamic CT[61], few studies have evaluated the accuracy of the technique for the diagnosis of metastatic lymph nodes. Ozaki[52] compared dynamic CT with plain CT for the diagnosis of lymph nodes in patients with gastric cancer and found that the sensitivity rate for localization by dynamic CT was slightly higher (92 per cent) than that by plain CT (88·5 per cent). Furthermore, they divided the visualized lymph nodes into enhanced and non-enhanced types and reported that 81·5 per cent of enhanced lymph nodes were non-malignant, whereas 98 per cent of non-enhanced lymph nodes were metastatic. Although the diagnostic accuracy of CT for lymph node staging of gastric cancer has improved, there are regions which are difficult to visualize clearly.

With recent improvement in diagnostic techniques, the rate of detection of early gastric cancers has increased annually, being over 50 per cent in some Japanese hospitals.

What is the optimum operation for gastric cancer?

In Japan, the principal surgical procedure for early gastric cancer is the R_2 resection with complete excision of groups 1 and 2 lymph nodes. The reason for this approach is that some patients with early gastric cancer show metastasis to the group 2 lymph nodes. Furthermore, accurate intraoperative determination of the presence or absence of lymph node metastasis is very difficult[62,63]. Unlike advanced cancer, haematogenous and disseminated metastases from early cancer are so rare that complete dissection of lymph nodes results in curative resection, with a favourable prognosis.

The rate of lymph node metastasis in early gastric cancer is low for mucosal cancers (0·6–11 per cent), but much higher for submucosal cancers (14·2–26·8 per cent)[1–4,9,47,48,64–66]. The rate of metastasis to group 1 lymph nodes was reported to be 0·7–4·7 per cent for mucosal cancers and 10·6–18·9 per cent for submucosal cancers. The rates of metastasis to group 2 lymph nodes were lower than those to group 1 lymph nodes being 0–2·4 per cent for mucosal cancers and 2·3–8·9 per cent for submucosal cancers. Metastasis to groups 3 or 4 lymph nodes may also occur but only in a very small number of patients[2–4,9,65,66]. Since lymphatic metastases are predicted to occur in only 3 per cent of mucosal cancers and about 20 per cent of submucosal cancers, the conventional view that the R_2 operation should be the standard surgical procedure may be questioned. It might be argued that a selective policy should be adopted depending on the depth of the primary. Suzuki *et al.*[2] compared the extent of lymph node dissection with survival rates. In the group without lymph node metastases there was no significant difference in survival rates according to extent of lymphadenectomy. In the group with lymph node

metastases the results of R_2 resection were significantly higher at 5–10 years than the R_1 operation[2].

There are few papers from Europe or North America with reference to lymph node clearance which can be compared with the Japanese data. However, Ribichini *et al.*[16] and Fass and Schumpelick[31] considered that the R_2 operation was necessary because of the incidence of metastasis in group 2 lymph nodes.

In view of the immunological function of lymph nodes[67–70] and the very favourable prognosis of early gastric carcinoma, a more limited lymphadectomy is being used more frequently[9,46,47,65,71–73]. However, the main dilemma lies in staging the depth of the primary tumour[12,74–76] since radical surgery would be indicated in many submucosal early gastric cancers[12,74–76]. Limited lymphadenectomy is more desirable for elderly high-risk patients.

Limited surgery[9,47,73] is defined as gastrectomy involving wide excision of the primary lesion while minimizing metabolic sequelae. There are no available guidelines for determining the extent of the gastrectomy. Limited surgery should probably not be performed unless the extent of the lesion and exclusion of a second primary can be assured. Furthermore, limited resection can only be justified if lymph node status is known. If the carcinoma cannot be accurately staged and the patient is fit, it is probably advisable to use the R_2 resection.

Low-risk factors for lymph node metastasis are cancers confined to the mucosa, the elevated type I and IIa lesions, small cancers and well differentiated adenocarcinoma[2,46,48,64,66,77,78]. For these types of early gastric cancer lymph node dissection can probably be limited to the R_1 operation. Some hospitals are already performing limited surgery for these groups[47,72], a policy that is expected to be used more widely as increasing numbers of patients with favourable early gastric cancer are picked up by preoperative screening.

Lymph node metastases are common in patients with submucosal or elevated early gastric cancer, particularly if they are 4 cm or more in diameter and are poorly differentiated with vascular invasion[1,2,4,9,12,64,65]. Women under 50 years tend to have unfavourable early gastric cancer[2]. In such patients the R_2 or R_3 operation, as for advanced cancers would be advised. The rate of recurrence following curative resection for early gastric cancers is very low but is higher for submucosal cancers (2·5–5·7 per cent) than for mucosal cancers (0·4–1·4 per cent)[7,9,66,79,80]. Recurrence is usually haematogenous, and the most frequent site is the liver[4,7,9,11,46,47,66,79–81]. Lymph node, bone, pulmonary and peritoneal metastases have been also reported[4,9,46,79–81]. Most recurrences occur within 5 years of operation[7,12,80,81].

Early gastric cancers which are most likely to recur are the IIa + IIc or elevated submucosal cancers, well differentiated tumours, those positive for lymph node metastasis or those in which there is vascular invasion[2,10–12,47,66,79–81]. The prognosis for aneuploid early gastric tumours was significantly worse than that for diploid tumours[82–84].

Surprisingly, differentiated early gastric cancers have more extensive lymph node metastases. Malignant cells frequently replace most of these nodes and invade the perinodal fatty tissue[77]. We believe that this high-risk group should be treated in the same way as those with advanced cancers, by means of complete lymph node dissection (R_2 or R_3) including the perinodal fatty tissue, using the no-touch isolation technique[85] or circulatory blockade to prevent haematogenous metastasis[47,80]. There are some who would argue in favour of postoperative adjuvant chemotherapy for this high-risk group[7,11,47,66,80,86].

Endoscopic surgery for early gastric cancer

Endoscopic surgery for the treatment of gastric cancer was first used in patients with severe co-existing medical disorders in whom resection was considered to be contraindicated or in those refusing surgery. Recently, some clinicians consider that for selected patients with early gastric cancer this procedure might be justified to achieve radical cure. The problem with endoscopic surgery is that staging must be very accurate because metastatic lymph nodes cannot be treated.

Minute lesions may be successfully treated, but large ones are difficult to cure completely by endoscopic therapy and require repeated treatments. Evaluation of the efficacy of treatment requires long-term follow-up with repeated biopsies. In addition, postoperative ulceration may enhance invasion to the deep layers by residual cancer cells. Radical endoscopic therapy is indicated only for patients who are thought to have no lymph node metastasis. Patients who are least likely to have lymph node involvement are those with elevated type I or IIa mucosal cancers of less than 2 cm diameter and those with IIc mucosal cancers less than 1 cm in diameter without an ulcer[12,73,87–89].

The following endoscopic methods are being used: (1) laser surgery[50,87,89,90]; (2) high frequency electric current polypectomy or strip biopsy known as mucosectomy[91–94]; (3) microwaves[95,96] and (4) local injections[97,98]. Of these, laser surgery is most widely used as it is easier than the other methods but requires expensive equipment. Strip biopsy or mucosectomy introduced by Tada *et al.*[92,99] was developed to obtain biopsies as large as 2–3 cm in diameter. The technique involves injections of physiological saline into the submucosa under the lesion to create a small swelling which is resected using a high frequency snare. This procedure permits resection of a block of tissue 1–2 cm in diameter. A further advantage is that histological examination of the resected specimen allows confirmation of the integrity of the resection and determination of vascular invasion as well as histological type of malignancy.

In 1986, Kasugai *et al.*[100] accumulated data on the endoscopic treatment of early gastric cancer from 71 hospitals; 1653 cases were studied and the proportion with no evidence of total recurrence for more than a year after treatment was 85 per cent for laser therapy and 99 per cent for high frequency therapy.

Endoscopic surgery is a valuable technique for elderly, poor risk patients and those refusing surgery, but must only be undertaken using strict criteria and careful follow-up if the aim of therapy is radical cure. This is because early gastric cancer can usually be cured by surgical treatment. For both endoscopic and conventional surgical excision, an accurate descriptive and histological diagnosis is essential to predict the likelihood of lymph node involvement and local infiltration which determines optimum therapy.

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