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Gen Thorac Cardiovasc Surg (2009) 57:71–78
DOI 10.1007/s11748-008-0337-5

CURRENT TOPICS REVIEW ARTICLE

Role of salvage esophagectomy after definitive chemoradiotherapy

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Received: 25 June 2008

Abstract Chemoradiotherapy has become a popular definitive therapy among many patients and oncologists for potentially resectable esophageal carcinoma. Although the complete response rates are high and short-term survival is favorable after chemoradiotherapy, persistent or recurrent locoregional disease is quite frequent. Salvage surgery is the sole curative intent treatment option for this course. As experience with definitive chemoradiotherapy grows, the number of salvage surgeries may increase. Selected articles about salvage esophagectomy after definitive chemoradiotherapy for esophageal carcinoma are reviewed. The number of salvage surgeries was significantly lower than the number of expected candidates. To identify candidates for salvage surgery, patients undergoing definitive chemoradiotherapy should be followed up carefully. Salvage esophagectomy is difficult when dissecting fibrotic masses from irradiated tissues. Patients who underwent salvage esophagectomy had increased morbidity and mortality. Pulmonary complications such as pneumonia and acute respiratory distress syndrome were common. The anastomotic leak rate was significantly increased because of the effects of the radiation administered to the tissues used as conduits. The most significant factor associated with long-term survival appeared to be complete resection. However, precise evaluation of resectability before operation was difficult. Nevertheless, increased morbidity and mortality will be acceptable in exchange for potential long-term survival after salvage esophagectomy. Such treatment should be considered for carefully selected patients at specialized centers.

Key words Esophageal cancer · Salvage surgery · Definitive chemoradiotherapy · Recurrence · Postoperative morbidity

Introduction

The standard treatment for potentially resectable esophageal carcinoma had been surgical resection. Despite many efforts to improve this method, the associated mortality and morbidity rates remain high and the postoperative quality of life is unsatisfactory. Poor outcome of surgical treatment alone has led to multidisciplinary approaches including radiotherapy and chemotherapy in combination with or without surgery.[1]

Preoperative chemoradiotherapy

Several studies showed a benefit of preoperative chemotherapy.[2,3] A recent meta-analysis showed no significant effect of preoperative chemotherapy on all-cause mortality for patients with squamous cell carcinoma, although there was a significant benefit for those with adenocarcinoma.[4] The higher pathological complete response rate after chemoradiotherapy (CRT), compared with chemotherapy alone, has led to a proposal of preoperative

This review was submitted at the invitation of the editorial committee.

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CRT. Despite the widespread use of preoperative CRT, randomized trials have yielded conflicting outcomes.[5–7] A survival benefit has not been satisfactorily demonstrated by means of a powered, prospective, randomized, controlled trial. The Cancer and Leukemia Group B trial (CALGB 9781) pointed to a survival benefit for neoadjuvant CRT compared with surgery alone recently, although only 56 of the expected 500 patients have been included.[8] The evidence only from meta-analyses had suggested a survival benefit.[4]

Some 15%–36% of surgical specimens have shown complete tumor eradication following preoperative CRT. The only long-term survivors from trials of preoperative CRT were patients who had no cancer in the surgically resected esophagus.[9] Patients treated with preoperative CRT with a plan to undergo esophagectomy can be conceptually categorized into three groups. The first group has had a pathological complete response after preoperative CRT. They are destined to do well without esophageal resection, and surgical intervention does not add value. The second group has had a partial response. Esophagectomy may cure some of these patients who are otherwise destined to have a recurrence. The third group has had little or no response to preoperative CRT. They are destined to do poorly irrespective of any treatment. This group of patients rarely benefit from additional esophagectomy. In this conceptual model, only a proportion of the second group of patients may benefit from surgery, but all three groups are subjected to the risks of surgery. Preoperative CRT decreases the rate of local failure and increases the rate of curative resection, but it also increases the morbidity rate, hence undercutting the benefit of surgery. If this conceptual model is valid, the addition of surgery to CRT cannot improve survival results of overall patients.

Two large randomized controlled trials examined whether surgery is necessary after CRT. In a German study, patients with locally advanced esophageal squamous cell carcinoma were randomly allocated to either CRT (40 Gy) followed by surgery or CRT (at least 65 Gy) without surgery.[10] Overall survival was equivalent between preoperative CRT with surgery and definitive CRT without surgery. Patients with surgery were less likely to die from cancer but had a significantly higher risk of treatment-related death compared with patients without surgery. A French trial of resectable squamous cell and adenocarcinoma randomized responding patients showing at least a partial response to CRT.[11] There was no benefit for the addition of surgery after CRT compared with the continuation of additional CRT. These results support the concept that CRT without planned surgery is as effective as the combination of neoadjuvant CRT followed by surgery.

Definitive chemoradiotherapy without planned surgery

The role of surgery as a curative modality had come into question. Trials that did not include surgery were designed.[12] The landmark Radiation Therapy Oncology Group trial (RTOG 85-01) for potentially resectable esophageal carcinomas has established CRT without surgery as one standard for definitive treatment.[13–15] Medical and radiation oncologists have reported comparable survival by definitive CRT without surgery with those reported for surgery alone. They have accepted the nonsurgical approach with CRT as definitive therapy for esophageal carcinoma, especially for squamous cell carcinoma. It is not surprising that many patients have chosen to undergo definitive CRT to preserve the upper digestive tract. The National Cancer Database of the American College of Surgeons have shown that radiation combined with chemotherapy is the most frequent treatment strategy for all stages of squamous cell carcinoma in the United States.[16] Also, definitive CRT without planned surgery has been offered to patients with potentially resectable and unresectable esophageal tumors in many Japanese institutions over the past decade.[17–21]

In an attempt to improve local control and overall survival, the chemotherapy and radiation doses were intensified.[22] However, adverse events have caused treatment-related deaths, even in complete response patients. The Intergroup 0123 not only found no improvement in survival in dose comparisons of 64.8 Gy versus 50.4 Gy of radiotherapy, respectively, but the effect on locoregional control did not improve.[23] Thus, the standard radiation dose for definitive CRT has become 50.0–50.4 Gy in the United States. Definitive CRT has mostly comprised combinations with a conventional radiation dose of >60.0 Gy in Japan.[17–21] Clinical trials for definitive CRT at a dose of 50.4 Gy are ongoing.

Candidates for salvage surgery after definitive chemoradiotherapy

Although CR rates are high and long-term survivals are 15%–30% after definitive CRT, locoregional recurrence is not uncommon, occurring in around 40%–60% of patients.[15] All patients with locoregional recurrence will die within 1 year without treatment. Furthermore, these patients have few other curative intent therapeutic options because they had already received maximal amounts of radiation, and additional chemotherapy would not control the recurrent locoregional disease. Many patients who had locoregional failure after definitive CRT also had distant failure, precluding surgical

resection for cure. However, there are patients who have an isolated local failure and may be suitable for surgical resection. The only curative intent treatment option for locoregional relapse is salvage surgery. The RTOG trial of definitive CRT reported that four patients underwent esophagectomy after CRT.[13]

As experience with definitive CRT grows, the number of patients referred to surgical departments for salvage surgery may increase.[24] The reported rate of salvage esophagectomy for patients in whom definitive CRT was used with curative intent has ranged from 4% to 29% (Table 1). The number of salvage surgeries was significantly lower than the number of expected candidates. The rate of salvage surgery was variable, reflecting a lack of criteria for the management of local failure in definitive CRT protocols. Wilson et al. planned selective esophagectomy for patients with post-treatment positive endoscopic biopsy or <75% regression on computed tomography (CT) scans and with resectable local recurrence.[27] Esophagectomy was performed in 11 of 32 patients after primary CRT. To detect candidates for salvage surgery as soon as possible, patients undergoing definitive CRT for potentially resectable tumors should be followed up carefully. Also, there are few available data on whether any patient declined salvage surgery after being informed of the risks of morbidity and mortality. Chao et al. reported 20 of 47 patients who had locoregional residual/recurrence tumor and underwent chemotherapy/supportive treatment due to unwillingness to receive surgery.[35]

Selected articles about salvage esophagectomy after definitive CRT for carcinoma of the esophagus are shown in Table 2. Whether a tumor is classified as persistent or recurrent may depend on the quality of the investigations during follow-up. The assessment to diagnose a complete response or persistent disease after CRT remains difficult. Nakamura et al. reported that three patients (11%) from the salvage group pathologically had a complete response.[31] These three patients complained of dysphasia caused by stricture of the esophagus. Nishimura et al. reported that, among 46 patients, 6 with a pathological complete response underwent salvage surgery.[34] Esophagectomy may be unnecessary after a complete response, but its diagnosis by imaging is difficult and possible only by esophageal resection. Endoscopic biopsies are notoriously inconclusive. Endoscopic ultrasonography or CT scans cannot distinguish postinflammatory changes and fibrosis from residual or recurrent carcinoma.[36,37] Recently, positron-emission tomography using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (PET-FDG) has been developed as a tool to assess tumor response to CRT,[36–38] but it cannot

Table 1 Rate of salvage esophagectomy after definitive chemoradiotherapy for esophageal carcinoma

Study	Duration	Histology	Chemotherapy	Radiation (Gy)	No. of CRT	No. of salvage esophagectomies
Leichman[12]	1983–1985	SCC	Cisplatin + 5-FU	50	20	3 (15%)
Herskovic[13]	1986–1990	SCC/adeno	Cisplatin + 5-FU	50	61	4 (7%)
Ishida[19]	1992–1994	SCC	Cisplatin + 5-FU	60	45	5 (11%)
Murakami[25]	1986–1998	SCC (T1, T2)	Cisplatin + 5-FU	70	32	2 (6%)
Murakami[26]	1984–1998	SCC (T3, T4)	Cisplatin + 5-FU	70	23	5 (22%)
Wilson[27]	1993–1998	SCC/adeno	Cisplatin + 5-FU	50	56	16 (29%)
Stahl[10]	1994–2002	SCC	Cisplatin + etoposide	50–60	77	5 (6%)
Smithers[28]	1988–2005	SCC/adeno	Cisplatin + 5-FU	60	253	11 (4%)

CRT, chemoradiotherapy; SCC, squamous cell carcinoma; adeno, adenocarcinoma; 5-FU, 5-fluorouracil

Table 2 Chemoradiotherapy and indications for salvage esophagectomy

Study	No. of patients	Duration	Histology	Chemotherapy	Radiation (Gy)	Persistent	Recurrent
Meunier[29]	6	1991–1995	SCC	Cisplatin + 5-FU	60	2	4
Wilson[27]	16	1993–1998	SCC/adeno	Cisplatin + 5-FU	50	10	6
Swisher[30]	13	1987–2000	SCC/adeno	Cisplatin + 5-FU	30–90	0	13
Nakamura[31]	27	1992–2002	SCC	Cisplatin + 5-FU	50–76	13	14
Tomimaru[32]	24	1985–2004	SCC	Cisplatin + adriamycin + 5-FU	62	13	11
Oki[33]	14	1994–2005	SCC	Cisplatin + 5-FU	60–70	5	9
Smithers[28]	14	1988–2005	SCC/adeno	Cisplatin + 5-FU	60	8	6
Nishimura[34]	46	2000–2006	SCC	Cisplatin + 5-FU	50.4–60.0	33	13
Chao[35]	27	1997–2004	SCC	Cisplatin + 5-FU	60	8	19

distinguish a complete response from small foci of residual tumors.[37]

Difficult aspects of salvage esophagectomy

Salvage esophagectomy after CRT is difficult when dissecting the indistinct planes between tumor and fibrotic masses within the irradiated tissues. Radiation injury causes early inflammation and late fibrosis. High total dose, large treatment fields, and large fractions cause more severe tissue injury. Patients undergoing salvage esophagectomy are treated with higher doses (50–70 Gy) of radiation than in the neoadjuvant setting. Salvage surgery is indicated many months after the completion of radiation therapy. The median interval between completion of CRT and salvage surgery was 4–18 months.

Meunier et al. reported that pleural adhesions and major bleeding from areas of postradiation fibrosis complicated the dissecting procedure so it was impossible to determine intraoperatively whether the procedure was curative or palliative.[29] Swisher et al. noted that the only factor found to be associated with perioperative mortality was the length of time to relapse.[30] This may have been due to the increased amount of fibrosis seen with time or to late esophageal changes after definitive CRT. Operative procedures for salvage esophagectomy after definitive CRT are shown in Table 3. The transthoracic approach was preferred for salvage esophagectomy supposed to depend on mediastinal fibrosis after irradiation.

Morbidity and mortality

Morbidity and mortality in salvage esophagectomy after definitive CRT are shown in Table 4. Salvage esophagectomy was associated with higher morbidity rates than esophagectomy after neoadjuvant CRT. Pulmonary complications such as pneumonia and acute respiratory distress syndrome (ARDS) were common. ARDS was associated with a high hospital mortality.[30,31,35] Tomimaru et al. described the period of time during which the patients fulfilled the systemic inflammatory response syndrome (SIRS) criteria was significantly longer in the salvage group than in the neoadjuvant group.[32] Patients

Table 3 Procedure of salvage esophagectomy

Study	No. of patients	Approach		Anastomosis		R0
		Transhiatal	Transthoracic	Thoracic	Cervical	
Meunier[29]	6	1	5		6	ND
Wilson[27]	16	NR	NR	NR	NR	NR
Swisher[30]	13	2	11	5	8	8
Nakamura[31]	27	4	23		27	18
Tomimaru[32]	24	7	17		24	16
Oki[33]	14	14		3	11	7
Smithers[28]	14	1	13	6	8	12
Nishimura[34]	46		46		46	46
Chao[35]	27		27	19	8	17

ND, not determined; NR, not reported

Table 4 Morbidity and mortality of salvage esophagectomy

Study	No. of patients	Morbidity (%)	Leakage (%)	Pulmonary complication (%)	Hospital stay (days)	30-Day mortality (%)	Hospital mortality (%)	Cause of hospital mortality
Meunier[29]	6	50	33	16	47 (mean)		16	Necrosis of the gastric tube
Wilson[27]	16		6		14 (median)	6	6	Intraoperative hemorrhage
Swisher[30]	13	77	38	38	29.4 (mean)	15	15	ARDS, leakage
Nakamura[31]	27		22	11	39.9 (mean)	4	7	ARDS, leakage
Tomimaru[32]	24	50	21	21		4	12	Peritonitis, hemoptysis
Oki[33]	14	50	36	21			7	Bleeding from tumor
Smithers[28]	14	79	14	57	31.5 (median)	7	7	
Nishimura[34]	46	54	22	9	47 (mean)	9	15	Leakage, pneumonia, arterial bleeding, tracheal necrosis, pneumonitis, cardiac
Chao[35]	27		15	33	22.4 (mean)	19	22.2	Leakage, ARDS

ARDS, acute respiratory distress syndrome

undergoing salvage esophagectomy had increases in the duration of ventilator support, which was reflected in prolonged stays in the intensive care unit and overall hospital stays.[28,30] Abou-Jawde et al. found that the diffusion capacity of the lung for carbon monoxide (DLCO) was the only pulmonary function test that changed significantly after preoperative CRT and was worse in the group receiving more radiation; a lower DLCO proved to be a significant predictor of postoperative acute respiratory complications, which in turn significantly reduced survival.[39]

Ischemic tracheobronchial lesions are serious complications of esophagectomy, particularly in patients undergoing surgery after CRT. Nakamura et al. reported a patient who died of tracheal bleeding caused by anastomotic leakage after reconstruction using the mediastinal route.[31] Tomimaru et al. reported three hospital deaths due to massive hemoptysis.[32] Nishimura et al. reported one hospital death due to trachea necrosis at 5 months.[34] Bartels et al. analyzed retrospectively prevalence and predisposing factors of nonmalignant lesions of the trachea or main stem bronchi in a consecutive series of esophagectomies.[40] On multivariate analysis, transthoracic en bloc resection and preoperative CRT for locally advanced tumors located at or above the level of the tracheal bifurcation predisposed to tracheobronchial fistula. Protective measures include preservation of the bronchial arteries during resection in addition to careful dissection around the airway.[41] For the salvage esophagectomy procedure, the right posterior bronchial artery should be preserved, and neck dissection should be avoided to preserve the blood supply from the inferior thyroidal artery to the trachea.

The anastomotic leak rate was also significantly increased in the salvage esophagectomy patients because of the effects of the radiation administered to the tissues used as conduits. The anastomotic leak rate in the reviewed papers varied between 6% and 38%. Oki et al. noted that leakage occurred more often when irradiation was performed in the locus used for the anastomosis.[33] Meunier et al. reported that an anterior gastroplasty had to be disconnected due to necrosis of the distal part of the gastric tube.[29] Chao et al. noted that three cases of fatal leakages occurred several weeks after surgery and were believed to be due to poor gastric perfusion as a result of high exposure of the proximal stomach to radiation.[35] After multivariate analysis, anastomosis leakage was the only independent significant perioperative risk factor. The increased risk of conduit necrosis and leakage may also be caused by patient factors, such as poor nutritional status and immunosuppression.

In an attempt to reduce the leak rates with salvage esophagectomy, possibilities include the use of jejunum with vascular anastomosis in the neck or colonic interposition. This technique would have the advantage of avoiding manipulation of the irradiated stomach. Sakuraba et al. performed an additional microvascular anastomosis at the distal end of the interposed colon. The distal stumps of the ileocolic artery and vein were anastomosed to the cervical vessels.[42] Subsequently, they had changed their reconstruction procedure, using a gastric tube restoring the short gastric artery and vein in the neck; then they used a gastric tube with only a short gastric vein restoration.[34]

The enterocutaneous fistulas from cervical anastomoses may be easier to control than mediastinal leaks. Chao et al. noted that three patients died of sepsis resulting from intrathoracic anastomosis leakage.[35] Swisher et al. reported a patient with a cervical anastomosis who died because of a leak from the lesser curvature into the thoracic cavity.[30] Modifications to reduce the impact of leaks into the thoracic cavity were suggested.

Salvage surgery after chemoradiation has been reported to be associated with a high hospital mortality rate (8%–15%). The causes of in-hospital death are also shown in Table 4. Nakamura et al. reported that because 2 of 14 (14%) patients who underwent three-field lymphadectomy died of postoperative complications less-

Table 5 Survival after salvage esophagectomy

Study	No. of patients	Survival (%)	Median survival (months)
Meunier[29]	6	0 (5 years)	7
Wilson[27]	16	37 (3 years)	16
Swisher[30]	13	25 (5 years)	NR
Nakamura[31]	27	31 (5 years)	18
Tomimaru[32]	24	33 (5 years)	NR
Oki[33]	14	14 (3 years)	NR
Smithers[28]	14	24 (3 years)	25
Nishimura[34]	46	17 (3 years)	22
Chao[35]	27	25.4 (5 years)	NR

NR, not reported

invasive procedures were performed and no hospital deaths were recorded thereafter.[31] The survival of patients who underwent less-invasive esophagectomy was similar to that of patients who underwent three-field lymph node dissection. Nishimura et al. reported that the patients who had cervical lymph node metastasis had poor outcomes, with all patients dying within 8 months.[34] The use of extended three-field lymphadenectomy should be restrained in salvage surgery.

Nishimura et al. had no hospital deaths after they changed the radiotherapy to 50.4 Gy from 60.0 Gy.[34] Swisher et al. noted that it is important that oncologists who choose to treat patients with definitive CRT do not use higher doses of radiation because these higher doses do not improve survival and would presumably increase the risks of salvage esophagectomy if needed.[30]

The incidence of acute toxicity of CRT seemed to be substantial. Furthermore, long-term or late cardiopulmonary toxicity cannot be ignored in patients who survive after CRT or in those who undergo salvage esophagectomy after CRT.[43,44] Nishimura et al. had one hospital death due to pneumonitis and another due to cardiac arrest during surgery.[34] A strategy to minimize the normal tissue toxicity of CRT should be identified.

Prognostic factors for salvage surgery

Survivals after salvage esophagectomy after definitive CRT are shown in Table 5. The most significant factor associated with long-term survival appeared to be resection without residual tumors (R0). No patient who had an incomplete resection (R1/R2) survived more than 13 months in any series. Swisher et al. reported that multivariate analysis indicated that the most significant factor appeared to be early pathological stage, although this was not statistically significant because of the overlap between early stage and R0 resection.[30] Smithers et al. also noted that R0 resection status correlated with improved long-term survival in a multivariate analysis. The survival of R0 patients was significantly better than that of R1/R2 patients.[27] Chao et al. also noted that a multivariate analysis revealed that R0 resection was the most important prognosticator for overall survival.[35]

However, accurate evaluation of the T factor in irradiated patients might be difficult preoperatively, and irradiated tissues are difficult to distinguish from tumors during surgery. Fibrosis is usually promoted in radiation fields, and some cancer cells are likely to be left behind in the deep layer of the esophageal wall after radiotherapy. Oki et al. reported that 7 of 14 patients underwent incomplete resection.[33] All seven cases of incomplete resection were T4 disease. Tomimaru et al. described eight patients who underwent a noncurative operation had an invaded airway.[32] Six patients were assessed by bronchoscopy preoperatively and were diagnosed to have no airway involvement.

There is some evidence of a more favorable cancer prognosis if salvage esophagectomy is done for recurrent disease than for persistent disease. Intuitively, this makes sense. Early salvage esophagectomy for persistent disease means a suboptimal response to CRT. Smithers et al. reported that the group who had recurrent disease had a longer median survival than patients who had residual disease.[27] In the M. D. Anderson experience, patients whose tumors were detected 12 months or more after CRT survived longer than those with earlier relapse, but this was not statistically significant on multivariate analysis.[30]

Conclusion

For esophageal squamous cell carcinoma, there are two options: preoperative chemotherapy or CRT with planned esophagectomy versus definitive CRT with esophagectomy used only if needed for persistent or recurrent local disease (salvage esophagectomy). Patients who underwent salvage esophagectomy after definitive CRT had high morbidity and mortality rates. Nevertheless, this is the only established treatment strategy that offers any chance of long-term survival. Five-year survival rates of up to 25%–35% can be achieved among selected patients treated by salvage esophagectomy. A high morbidity rate is acceptable in view of the potential for long-term survival after salvage esophagectomy. Patients should be carefully selected for salvage esophagectomy after CRT at referral centers that specialize in esophageal cancers.

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Esophagus (2007) 4:103–110
DOI 10.1007/s10388-007-0122-7

ORIGINAL ARTICLE

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A new N category for cancer in the esophagogastric junction based on lymph node compartments

Received: March 30, 2007 / Accepted: July 27, 2007

Abstract
Background. There remains controversy as to which lymph nodes should be or need to be resected to cure patients with a cancer in the esophagogastric junction (EGJ).
Methods. A series of 1289 patients with a cancer in the EGJ are reviewed in this study. Cancers in the EGJ were divided in two groups, as esophagus-dominant tumors or stomach-dominant tumors, and the regional lymph nodes of each group were classified into three compartments (N category) using a score obtained by multiplication of the metastatic rate by the 5-year survival rate after lymphadenectomy.
Results. The N1 nodes for an esophagus-dominant tumor were the right and left cardiac (1, 2), the lesser curvature (3), the left gastric artery (7), the esophageal hiatus (20), and the lower thoracic paraesophageal nodes (110). The N2 nodes were the anterosuperior group of the common hepatic artery (8a), the celiac (9), the splenic artery (11), the infradiaphragmatic (19), the middle thoracic paraesophageal (108), the right and left pulmonary hilar (109), and the supradiaphragmatic nodes (111). The N3 nodes were the greater curvature (4sa, 4sb, 4d), the suprapyloric and subpyloric (5, 6), the right and left recurrent nerve (106rec), the infracarinal (107), and posterior mediastinal nodes (112). The N1 nodes for a stomach-dominant tumor were the 1, 2, 3, 7, and 20 nodes. The N2 nodes were the 8a, 9, 11, 4sa, 4sb, and 19 nodes. The N3 nodes were the 4d, 5, 6, the posterior group of the common hepatic artery (8p), the splenic hilar (10), the abdominal paraaortic (16a2/b1), 20, 108, 110, 111, and 112 nodes.
Conclusions. A new N category for cancer in the EGJ was proposed based on the metastatic rates of the lymph nodes and the survival rates.

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Key words N category · Cancer in the esophagogastric junction · Cardia cancer · Lymph node compartment · Lymphadenectomy

Introduction

There remains controversy over whether a cancer in the esophagogastric junction (EGJ) should be considered as a distinct clinical entity. Many surgeons now recognize these cancers as a distinct entity different from esophageal cancer or gastric cancer [1,2]. In the *TNM classification of malignant tumors* of the International Union Against Cancer (UICC, 2002) [3], the cardia – the area of the EGJ – is classified as an anatomical subsite of the stomach. In this classification, the regional lymph nodes of the EGJ are defined to be the paracardial, left gastric, celiac, diaphragmatic, and the lower mediastinal paraesophageal nodes, being different from the regional lymph nodes of the stomach. Also, in *Guidelines for clinical and pathologic studies on carcinoma of the esophagus* of the Japanese Society for Esophageal Diseases (JSED, 1999) [4], the regional lymph nodes for a tumor located in the EGJ (EG, E = G, GE) are distinguished from those for esophageal tumors in other locations. There have been many reports that have described the distribution of lymph node metastasis from cancers in the EGJ, or cardia cancers [2,5–8]. On the other hand, others still consider that a cancer in the EGJ is not a distinct entity, because it resembles a proximal gastric cancer (Siewert type III) [6]. Also in *Japanese classification of gastric carcinoma* of the Japanese Research Society for Gastric Cancer (JRSGC, 1995) [9], the cardia – the area of the EGJ – was not specified, and the lymph nodes that should be resected were added to the regional lymph nodes of the upper gastric cancer only when it involved the esophagus. Accordingly, the definitions of the regional lymph nodes of the EGJ remain various, as does the definition of a cancer in the EGJ. There is therefore no consensus yet over what constitutes rational lymphadenectomy for a cancer in the EGJ.

We have proposed a new N category for a cancer in the EGJ based on the idea of lymph node compartments [10,11]. This concept is based on the incidence of metastasis to each cluster of regional lymph nodes of cancers in the EGJ and on the survival rates after resection of the lymph nodes in each cluster, as reported by Sasako et al. [12], who proposed their own N category for gastric cancers. The lymph node compartments are defined as follows; compartment-I lymph nodes have frequent metastasis, and patients with metastasis in these nodes have a good prognosis after lymphadenectomy; compartment-III lymph nodes have rare metastasis, and patients with metastasis in these nodes have a poor prognosis even if the lymph nodes are resected; compartment-II lymph nodes have an intermediate frequency of metastasis and prognosis. We consider that the concept of lymph node compartments can be applied as adequate guidelines for lymphadenectomy. The compartment-I lymph nodes should be resected in every case. The compartment-II lymph nodes should be resected as far as practicable, and the compartment-III lymph nodes need not be resected if a patient is at high risk for mortality and morbidity. Compartment-IV lymph nodes, which include all those not in compartments-I–III, rarely present any metastasis, and are not considered to be regional lymph nodes.

The purpose of this study was to propose a new N category for a cancer in the EGJ, using multi-institutional data, that indicated more clearly which cluster(s) of lymph nodes should be resected during resection of a cancer in the EGJ. The new N category for a cancer in the EGJ will be useful to describe the extent of lymph node metastasis, as well as providing guidelines for reasonable lymphadenectomy in cancers in the EGJ [4,9].

Definition of the EGJ and cancer in the EGJ

The EGJ was defined as the portion where the diameter changed from the shorter one of the esophagus to the wider one of the stomach in the resected specimen. A cancer in the EGJ in this study was defined as a tumor that has its center located between 2 cm proximal and 2 cm distal from the EGJ according to the Nishi classification [13].

Cancers in the EGJ were classified into two groups; an esophagus-dominant tumor, a squamous cell carcinoma (SCC) the center of which was situated in the esophagus or just on the EGJ (E ≧ G) plus an adenocarcinoma (AD) the center of which was situated in the esophagus (E > G); and a stomach-dominant tumor, an AD the center of which was situated in the stomach or just on the EGJ (E ≦ G) plus a SCC the center of which was situated in the stomach (E < G), as shown in Fig. 1.

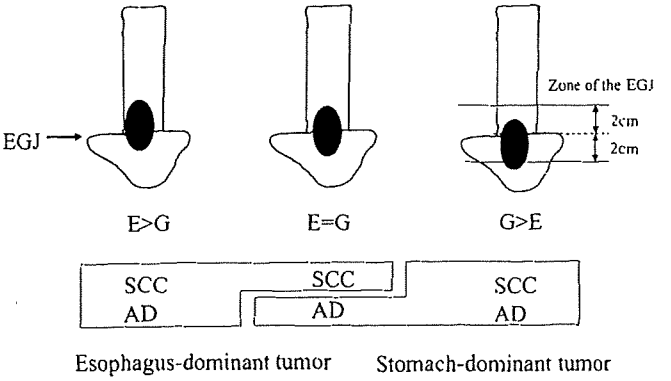

Fig. 1. Definition of the esophagogastric junction (*EGJ*) and cancers in the EGJ. *E*, Esophageal portion; *G*, gastric portion; *SCC*, squamous cell carcinoma; *AD*, adenocarcinoma

Patients and methods

Study population

During the 10 years from 1990 to 1999, 2073 patients who underwent resection of a cancer in the EGJ were registered into our nationwide inquiry research at 98 institutes belonging to the Japanese Society for Esophageal Diseases [7]. Among these, 1532 patients were reviewed when excluding the patients with a tumor of histopathological type other than SCC or AD, those who did not undergo R0 curative resection, and those who did not undergo systemic lymphadenectomy, which meant D > 0 lymphadenectomy according to the *Japanese classification of gastric carcinoma* [9] and the *Guidelines for clinical and pathological studies on carcinoma of the esophagus* [4]. In addition, the patients with a tumor more than 7 cm in length were excluded. Consequently, the number of subjects in this study was reduced to 1289. Barrett's epithelium was observed in 55 (5.3%) of the patients. There were 465 (36.1%) cases of SCC, and 824 (63.9%) of AD. Neoadjuvant therapy was performed for 6.6% of patients, while adjuvant therapy was performed for 34.1%. The thoracoabdominal approach was adopted for 53.2% of patients, and the mediastinoabdominal or abdominal approach for 46.8%. Subtotal esophagectomy was performed for 25.4% of patients, and lower esophagectomy was done for 65.2% of patients. Total gastrectomy was adopted for 49.0% of patients, and proximal gastrectomy for 48.7%.

The 30-day mortality rate was 0.9% (11/1289), and the hospital mortality rate including the 30-day mortality was 2.0% (25/1279). The cumulative survival rates of all the patients were calculated by Kaplan-Meier analysis. The 5-year survival rate was 57.9%, and the 10-year survival rate was 49.6% (Fig. 2). The clinical characteristics of the esophagus-dominant tumors and the stomach-dominant tumors in the EGJ are shown in the Table 1.

Terminology of the regional lymph nodes of the EGJ

The terminology of the lymph nodes is shown in Table 2, authorized by the Japanese Research Society for Gastric Cancer [9] and the Japanese Society for Esophageal Diseases [4].

Table 1. Clinical characteristics of 1289 patients who underwent resection of a cancer in the EGJ

Characteristic	EG (n = 523)	GE (n = 766)
Average age	63.3 ± 7.7 years	64.3 ± 11.2 years
Male	432	591
Female	90	175
Average length of tumor	4.2 ± 1.6 cm	4.0 ± 1.7 cm
Squamous cell carcinoma	393	72
Adenocarcinoma	130	694
Barrett's epithelium		
+	34	21
–	400	577
nd	89	168
TNM staging[a]		
pT		
TisT1a	26	79
T1b	109	146
T2	85	185
T3	278	328
T4	20	25
n	5	3
pN		
N0	214	364
N1[b]	307	360
nd	2	42
pM-Org		
M0	487	724
M1[c]	13	15
nd	23	27
R[d]		
R0	523	766
R1R2	0	0
nd	0	0
Adjuvant therapy		
Preoperative		
+	52	31
–	465	719
nd	6	16
Postoperative		
+	182	225
–	324	461
nd	17	80
Surgical procedures		
Approach		
rtTA	258	64
ltTA	152	209
MA	83	321
Other	26	170
nd	4	2
Esophagectomy		
Subtotal	267	59
Lower	247	590
None	7	114
nd	2	3
Gastrectomy		
Total	144	478
Proximal	351	268
None	12	17
nd	16	3

EG, Esophagus-dominant tumor; GE, stomach-dominant tumor, rtTA, right thoracoabdominal; ltTA, left thoracoabdominal; MA, mediastinoabdominal; nd, no data

[a] International Union Against Cancer [3]

[b] Including M1-Lym

[c] Excluding M1-Lym

[d] Residual tumor classification

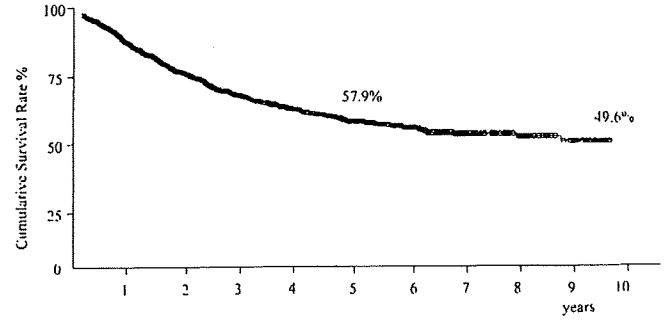

Fig. 2. The cumulative survival curve of 1289 patients who underwent resection of a cancer in the EGJ

Lymph node compartment classification

The frequency of metastasis was examined in each cluster of lymph nodes, and the survival rates for each were calculated by Kaplan-Meier analysis for all patients with metastasis in each cluster of lymph nodes. Based on the simple value obtained by multiplying the percentage rate of positive metastasis (a) by the 5-year survival rate (b), the lymph nodes were classified into four groups. The lymph nodes with an $a \times b$ value of more than 0.05 were classified as compartment-I; those with an $a \times b$ value between 0.05 and 0.02 were classified as compartment-II; and those with an $a \times b$ value between 0.02 and 0.005 were classified as compartment-III. Compartment-III was divided into two groups; IIIA with an $a \times b$ value between 0.01 and 0.02, and IIIB with an $a \times b$ value between 0.005 and 0.01. The lymph nodes with an $a \times b$ value of less than 0.005 were excluded from being regional nodes in EGJ cancer, and are considered as being distant nodes in compartment-IV (Table 3).

Results

The incidences of lymph node metastasis from esophagus-dominant tumors in the EGJ are shown in Table 4. The metastatic rate for each cluster of lymph nodes was calculated as the ratio of the number of patients with metastasis in each cluster of lymph nodes to the total number of patients (n = 523) registered. The lower thoracic paraesophageal nodes (110), the right and left cardiac nodes (1, 2), the lesser curvature nodes (3), and the left gastric artery nodes (7) frequently presented positive metastasis, while the cervical and upper mediastinal nodes, and the abdominal paraaortic nodes were rarely involved. The metastatic rates to those nodes were less than 5%. The 5-year survival rate after resection of the metastatic lymph nodes was high in those patients with metastasis to the upper and lower mediastinal nodes (106–112), the perigastric nodes (1–6), and the abdominal nodes (7–11, 16, 19), while there was rarely 5-year survival in patients with metastasis to the cervical nodes.

The incidences of lymph node metastasis from stomach-dominant tumors in the EGJ (n = 766) are shown in

Table 2. Terminology of the regional lymph nodes of a cancer in the esophagogastric junction authorized by the Japanese Gastric Cancer Association and the Japanese Society for Esophageal Diseases

Cervical lymph nodes	Thoracic lymph nodes	Abdominal lymph nodes
100 Superficial cervical	105 Upper thoracic paraesophageal	1 Right cardiac
101 Cervical paraesophageal	106 Thoracic paratracheal	2 Left cardiac
102 Deep cervical	106rec Recurrent nerve	3 Lesser curvature
102u Upper deep cervical	106pre Pretracheal	4 Greater curvature
102m Middle deep cervical	106tb Tracheobronchial	4sa Along the short gastric vessels
103 Peripharyngeal	107 Bifurcational	4sb Along the left gastroepiploic vessels
104 Supraclavicular	108 Middle thoracic paraesophageal	4d Along the right gastroepiploic vessels
	109 Main bronchus	5 Suprapyloric
	110 Lower thoracic paraesophageal	6 Subpyloric
	111 Supradiaphragmatic	7 Left gastric artery
	112 Posterior mediastinal	8 Common hepatic artery
	113 Ligamentum arteriosus	8a Anterosuperior group
	114 Anterior mediastinal	8p Posterior group
		9 Coeliac artery
		10 Splenic hilar
		11 Splenic artery
		12 Hepatoduodenal ligament
		13 Posterior surface of the pancreatic head
		14 Root of the mesenterium
		14a Superior mesenteric artery
		14v Superior mesenteric vein
		15 Middle colic vessels
		16 Abdominal paraaortic
		16A Above the renal vein
		16B Below the renal vein
		17 Anterior surface of the pancreatic head
		18 Infrapancreatic
		19 Infradiaphragmatic
		20 Esophageal hiatus

Table 3. Compartment classification using the product of metastatic rate (a) in the regional lymph nodes and the 5-year survival rate (b) after resection of the nodes

Compartment	$a \times b$ score range	Characteristics
I	≥0.05	Frequent metastasis, good prognosis after lymphadenectomy Should be resected in every case
II	0.02–0.05	Intermediate frequency of metastasis and prognosis Should be resected as far as practicable
IIIA	0.01–0.02	Rare metastasis, poor prognosis after lymphadenectomy Need not be resected if a patient is at high risk for mortality and morbidity
IIIB	0.005–0.01	
IV	<0.05	Distant metastasis Need not be resected in any case

Table 5. The right and left cardiac nodes (1, 2), the lesser curvature nodes (3), and the left gastric artery nodes (7) frequently presented positive metastasis, while the cervical nodes, the upper and lower mediastinal nodes, and abdominal paraaortic nodes were rarely involved. The 5-year survival rate after resection of the metastatic lymph nodes was high in those patients with metastasis to the cervical nodes (101), the upper and lower mediastinal nodes (106, 108, 112), the perigastric nodes (1–6), and the abdominal nodes (7–14, 16, 19, 20).

The values obtained by multiplying the metastasis (a) by the 5-year survival rate (b) are also described in Tables 4 and 5. Figures 3 and 4 illustrate the proposed new N category for a cancer in the EGJ based on the lymph node compartments. For an esophagus-dominant tumor, the compartment-I (N1) nodes are the lower thoracic paraesophageal nodes (110), the right and left cardiac nodes (1, 2), the lesser curvature nodes (3), the left gastric artery nodes (7), and the esophageal histus nodes (20). The compartment-II (N2) nodes are the middle thoracic paraesophageal nodes (108), the supradiaphragmatic nodes (111), the anterosuperior group of the common hepatic artery nodes (8a), the celiac nodes (9), the splenic artery nodes (11), and the infradiaphragmatic nodes (19). The compartment-III (N3) nodes are the recurrent nerve nodes (106rec), the bifurcational nodes (107), the main bronchus nodes (109), the posterior mediastinal nodes (112), the greater curvature nodes (4sa, 4sb, 4d), and the suprapyloric and subpyloric nodes (5, 6). For a stomach-dominant tumor, the compartment-I (N1) nodes are the right and left cardiac nodes (1, 2), the lesser

Table 4. Incidences of metastasis (*a*) in each cluster of the lymph nodes and the 5-year survival rates (*b*) of patients with metastasis in a particular cluster of the lymph nodes for an esophagus-dominant tumor in the esophagogastric junction

Cluster	Incidence	*a*	*b*	*a* × *b*	Compartment	Cluster	Incidence	*a*	*b*	*a* × *b*	Compartment
100R	2	0.4%	0%	0		1	176	33.7%	39.2%	0.132	I
100L	2	0.4	0	0		2	122	23.3	32.7	0.076	I
101R	6	1.1	16.7	0.002		3	116	22.2	36.3	0.081	I
101L	6	1.1	25.0	0.003		4sa	11	2.1	25.6	0.005	IIIB
102uR	3	0.6	0	0		4sb	8	1.5	58.3	0.009	IIIB
102uL	2	0.4	0	0		4d	8	1.5	50.0	0.008	IIIB
102mR	1	0.2	0	0		5	8	1.5	50.0	0.008	IIIB
102mL	2	0.4	0	0		6	6	1.1	83.3	0.010	IIIA
103	2	0.4	0	0		7	99	18.9	36.1	0.068	I
104R	5	1.0	0	0		8a	35	6.7	32.8	0.022	II
104L	6	1.1	0	0		8p	1	0.2	0	0	
105	11	2.1	0	0		9	30	5.7	34.9	0.020	II
106recR	24	4.6	21.6	0.010	IIIA	10	2	0.4	50.0	0.002	
106recL	12	2.3	33.3	0.008	IIIB	11	29	5.5	46.1	0.026	II
106pre	4	0.8	0	0		12	1	0.2	0	0	
106tbL	11	2.1	20.8	0.004		13	0	0	–		
107	20	3.8	25.4	0.010	IIIA	14a	1	0.2	0	0	
108	35	6.7	36.6	0.024	II	14v	1	0.2	0	0	
109R	15	2.9	28.3	0.008	IIIB	15	0	0	–		
109L	12	2.3	30.0	0.007	IIIB	16A	5	1.0	40.0	0.004	
110	75	14.3	35.1	0.050	I	16B	1	0.2	0	0	
111	35	6.7	55.7	0.037	II	17	0	0	–		
112	28	5.4	29.9	0.016	IIIA	18	0	0	–		
113	0	0	–			19	3	0.6	66.7	0.004	
114	0	0	–			20	7	1.3	0	0	

Table 5. Incidences of metastasis (*a*) in each cluster of the lymph nodes and the 5-year survival rates (*b*) of patients with metastasis in a particular cluster of the lymph nodes for a stomach-dominant tumor in the esophagogastric junction

Cluster	Incidence	*a*	*b*	*a* × *b*	Compartment	Cluster	Incidence	*a*	*b*	*a* × *b*	Compartment
100R	0	0%	–%			1	230	30.0%	46.6%	0.140	I
100L	0	0	–			2	152	19.8	46.8	0.093	I
101R	1	0.1	100	0.001		3	191	24.9	40.0	0.100	I
101L	0	0	–			4sa	46	6.0	50.2	0.030	II
102uR	0	0	–			4sb	28	3.7	77.2	0.028	II
102uL	0	0	–			4d	20	2.6	59.2	0.015	IIIA
102mR	0	0	–			5	23	3.0	59.9	0.018	IIIA
102mL	0	0	–			6	18	2.3	69.2	0.016	IIIA
103	0	0	–			7	131	17.1	32.3	0.055	I
104R	0	0	–			8a	50	6.5	50.7	0.033	II
104L	0	0	–			8p	7	0.9	19.1	0.002	
105	1	0.1	0	0		9	52	6.8	39.2	0.027	II
106recR	2	0.3	100	0.003		10	30	3.9	32.8	0.013	IIIA
106recL	0	0	–			11	59	7.7	37.2	0.029	II
106pre	0	0	–			12	5	0.7	40.0	0.003	
106tbL	2	0.3	0	0		13	3	0.4	66.7	0.003	
107	0	0	–			14a	1	0.1	100	0.001	
108	11	1.4	43.6	0.006	IIIB	14v	2	0.3	100	0.003	
109R	0	0	–			15	0	0	–		
109L	0	0	–			16A	19	2.5	27.2	0.007	IIIB
110	43	5.6	19.3	0.011	IIIA	16B	10	1.3	29.6	0.004	
111	24	3.1	18.8	0.006	IIIB	17	0	0	–		
112	9	1.2	57.1	0.007	IIIB	18	0	0	–		
113	0	0	–			19	4	0.5	75.0	0.004	
114	0	0	–			20	8	1.0	62.5	0.007	IIIB

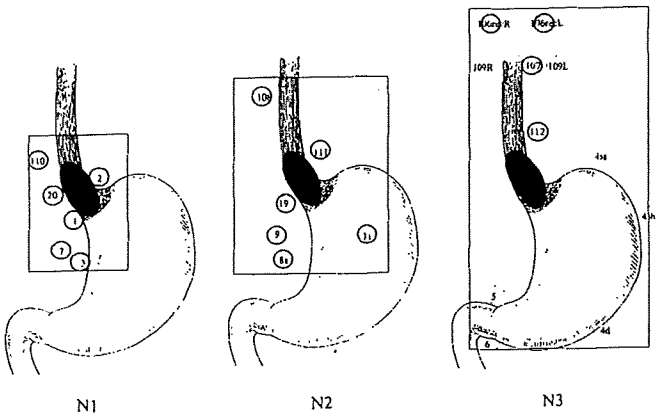

Fig. 3. The new N category for an esophagus-dominant tumor in the EGJ based on lymph node compartments. *Dotted circles*, lymph nodes for which dissection can be omitted under certain circumstances

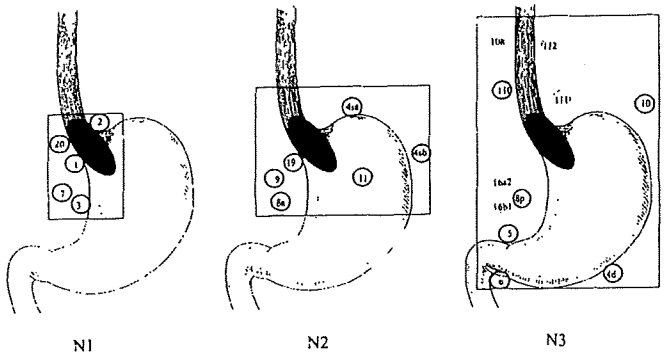

Fig. 4. The new N category for a stomach-dominant tumor in the EGJ based on the lymph node compartments. *Dotted circles*, lymph nodes for which dissection can be omitted under certain circumstances

curvature nodes (3), the left gastric artery nodes (7), and the esophageal hiatus nodes (20). The compartment-II (N2) nodes are the greater curvature nodes (4sa, 4sb), the antero-superior group of the common hepatic artery nodes (8a), the celiac nodes (9), the splenic artery nodes (11), and the infradiaphragmatic nodes (19). The compartment-III (N3) nodes are the middle and lower paraesophageal nodes (108, 110), the supradiaphragmatic nodes (111), the posterior mediastinal nodes (112), the greater curvature nodes along the right gastroepiploic vein (4d), the suprapyloric and subpyloric nodes (5, 6), the posterior group of the common hepatic artery group (8p), the splenic hilar nodes (10), and the abdominal paraaortic nodes (16a2, 16b1).

Discussion

There remains controversy over how to define a cancer in the EGJ – a cardia cancer. There are two definitions for a cancer in the EGJ: the Siewert classification [14] and the Nishi classification [13]. In the Siewert classification, true cardia cancer is limited to adenocarcinoma with its center situated between 1 cm proximal and 2 cm distal from the anatomical EGJ. On the other hand, according to the Nishi classification, a cancer in the EGJ is a tumor of any histological type with its center situated between 2 cm proximal and 2 cm distal from the anatomical EGJ. Misumi et al. [15] reported that the cardiac gland area was the buffer zone between the squamous epithelium in the esophagus and the fundic glands area in the stomach, and this was found to straddle the EGJ at the range of 1 cm proximal and 2 cm distal from the junction. They therefore proposed that carcinoma of the gastric cardia be defined as a lesion with its center located within 1 cm proximal and 2 cm distal from the EGJ, for any histologic type. On the other hand, because the length of the abdominal esophagus between the upper margin of the esophageal hiatus and the EGJ is around 2 cm, Nishi et al. [13] have supported that the zone of the EGJ, the cardia, was the portion between 2 cm proximal and 2 cm distal from the junction.

In our inquiry research, the average length of cancers in the EGJ was 4.7 ± 1.9 cm. Therefore, we limited the subjects of our investigation to those with cancers of 7 cm or less in diameter. We considered that when the tumor length was too large, lymph node metastasis spread more widely, so that any distinct pattern in lymph node metastasis from a cancer in the EGJ would become unclear. Consequently, the subjects decreased from 1532 to 1289 patients (84.1%), when tumors of more than 7 cm in length were excluded. The conclusion from the present study may be true only for localized cancers in the EGJ, and not for invasive or large cancers.

The present study included only squamous cell carcinoma and adenocarcinoma. This was because we considered that when the tumors were located in the same portion, the patterns of lymph node metastasis and the long-term prognosis were similar for any histopathological type [16]. During the registration period from 1990 to 1999, most Japanese surgeons held a different view from that cited above. Most squamous cell carcinomas in the EGJ were operated on by esophageal surgeons who commonly performed either subtotal esophagectomy through a right thoracotomy or lower esophagectomy through a left thoracotomy with esophageal reconstruction using the stomach. In contrast, most adenocarcinomas in the EGJ were operated on by gastric surgeons who commonly performed partial esophagectomy with total gastrectomy through a mediastinoabdominal approach, and esophageal reconstruction using the jejunum. Accordingly, total or lower mediastinal and upper abdominal lymphadenectomy was performed for a squamous cell carcinoma, and occasionally cervical lymphadenectomy was added, while lower mediastinal and upper abdominal lymphadenectomy was performed for an adenocarcinoma, and occasionally dissection for abdominal paraaortic nodes was added. However, as the incidence of adenocarcinoma in the Barrett esophagus increased, this concept has become unsuitable in practice. Our new concept is that lymphadenectomy should be done according to the tumor location rather than the tumor histology. Therefore, we have proposed a new N category based on tumor locations.

We have accordingly investigated and here have proposed a new N category based on the idea of lymph node

compartments in which regional lymph nodes are classified into the three compartments: compartment-I (N1), compartment-II (N2), or compartment-III (N3). Other nodes (N4) were considered to be distant from the EGJ. Based on this concept, the extent of lymph node metastasis (N category) was determined rationally. We consider that the extent of lymph node metastasis should be expressed not only quantitatively by the number of the metastatic lymph nodes, but also qualitatively according to the spread of lymph node metastases. The new N category is also useful to express the extent of lymph node dissection as a D grading. In the Japanese guidelines for esophageal cancer and gastric cancer [4,9], the D grading (the extent of lymph node dissection) is required to be larger than the N grading (the spread of lymph node metastasis) for complete R0 resection of cancers.

The definition of each lymph node compartment and the significance of the multiplicity values are described in Table 3. We consider that the multiplicity value indicates the efficacy of lymph node dissection [11,12]. The multiplicity value varies with the 5-year survival rate and with the observed metastatic rate. Moreover, it should be noted that the criteria for classifying lymph node compartments are changeable according to the disease, institution, and other factors. The multiplicity values described in Table 3 are values derived empirically in our studies in order to illustrate the basis for proposing the N category for cancer in the EGJ using the registration data of those cancers operated during the period from 1990 to 1999 in many Japanese institutions. These multiplicity values are therefore specific only to our study and will need further studies to be confirmed for wider generalization.

There are discrepancies in the N categories of No. 19 and No. 20 lymph nodes, between the new N category shown in Table 6 and the lymph node compartment classification based on the multiplicity values of the metastatic rate and the 5-year survival rate shown in Tables 4 and 5. Our data include those cases that underwent operation during the period from 1990 to 1999. However, the lymph nodes No. 19 and No. 20 were at first defined in the 12th edition of the *General rules for the gastric cancer study* published in 1993 [17]. Before 1993, the No. 19 lymph nodes might be classified as being in other lymph node groups, for example, the No. 2 nodes, while the No. 20 lymph nodes might be classified as being included in among the No. 110 nodes. The No. 19 and No. 20 nodes have low frequencies of metastasis in the data, and have low multiplicity values from the metastatic rates and the 5-year survival rates. The existence and significance of these nodes should be reevaluated in future studies.

According to the new N category for an esophagus-dominant tumor, the compartment-I (N1) and compartment-II (N2) nodes can be resected by lower esophagectomy with proximal gastrectomy through a left thoracoabdominal approach. Compartment-I (N1) and compartment-II (N2) nodes for a stomach-dominant tumor can be resected by partial esophagectomy with proximal gastrectomy through a mediastinoabdominal approach – extended radical gastrectomy [6,14]. On the other hand, in order to resect compartment-III (N3) nodes for an esophagus-dominant tumor, subtotal esophagectomy with total gastrectomy through a right thoracoabdominal approach is required, and then colon interposition is needed for esophageal reconstruction. In order to resect compartment-III (N3) nodes for a stomach-dominant tumor, total gastrectomy with lower esophagectomy through a left thoracoabdominal approach is required. Complete dissection of those mediastinal lymph nodes including the compartment-III is difficult to achieve through a transhiatal approach – mediastinoabdominal approach. However, compartment-III (N3) lymph nodes need not be resected if a patient is at high risk for mortality and morbidity because of the low incidence of metastasis and poor prognosis in any case after resection of these nodes. In this new N category, we have indicated some of the N3 nodes for which lymphadenectomy can be omitted because of the low value of the metastatic rate multiplied by the 5-year survival rate.

The new N category is compared with the N category in the Japanese guidelines for esophageal cancer [4] and with that in the Japanese guidelines for gastric cancer [9] (Table 6). A majority of the lymph nodes were classified into the same N grading. The new N categories for an esophagus-dominant tumor (EG) and a stomach-dominant tumor (GE) of cancers in the EGJ are respectively similar to the N categories of cancers in the abdominal esophagus (Ae)

Table 6. Comparison among N categories for cancer in the esophagogastric junction

N category	New N category		JSED		JRSGA
	EG	GE	Ae	EG/E=G/GE	U + E
Compartment-I N1	110,1,2,3,7,20	1,2,3,7,20	1,2,3,20	1,2,3	1,2,3,4sa,4sb,20
Compartment-II N2	108,111,8a,9,11,19	4sa,4sb,8a,9,11,19	110,111,(4),7,9, (10),(11),19	(110),(111),(4),7,9, 10,11	4d,7,8a,9,10,11,19
Compartment-III N3	106rec,107,(109) 112,(4sa),(4sb),(4d) (5),(6)	(108),110,(111),(112) 4d,5,6,8p,10 (16a2),(16b1)	108,5,8,(112)	108,(112),5,6,8,(12), (13),(14)	110, 111,112,5,6, 8p,12,16a2,16b1

Figures in parentheses indicate lymph nodes for which dissection can be omitted under certain circumstances
JSED, Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (Japanese Society for Esophageal Diseases); JRSGA, Japanese Classification of Gastric Carcinoma (Japanese Research Society for Gastric Cancer); EG, esophagus-dominant tumor; GE, stomach-dominant tumor; Ae, abdominal esophagus; EG/E=G/GE, tumor located at the esophagogastric junction; U+E, upper gastric cancer with esophageal invasion

and those located in the EGJ with respect to the Japanese guidelines for esophageal cancer [4]. On the other hand, the N category of an upper gastric cancer with esophageal invasion (U + E) in the Japanese guidelines for gastric cancer [9] regards the perigastric and abdominal paraaortic nodes as more important. When it is verified that this new N category for a cancer in the EGJ is more rational than that for a cancer located in the EGJ with the Japanese guidelines of esophageal cancer [4], the new N category may replace the N-grading of a cancer in the EGJ in the guidelines.

Acknowledgments The authors are deeply indebted to the 98 medical institutions that registered cancers of the esophagogastric junction at the 54th Study Meeting of the Japanese Society for Esophageal Diseases (JSED) in 2000. The authors also thank: Professor Hiroko Ide, who organized the registration and research as the Congress President of the 54th Meeting of the JSED in 2000; Professor Yuzo Uchida, who initiated this research as the former Chairman of the Committee for the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus; Professor Kaichi Isono, who supported this registration and research as the President of the JSED; and Professor Hiroki Inutsuka, Information Education Center, Kurume University School of Medicine, who supported this research with statistical analysis.

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Gynecologic Oncology 115 (2009) 488–492

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Prognostic significance of positive peritoneal cytology in adenocarcinoma of the uterine cervix

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ARTICLE INFO

Article history:
Received 17 June 2009
Available online 19 September 2009

Keywords:
Peritoneal cytology
Adenocarcinoma
Cervical cancer
FIGO stage IB to IIB
Risk factor

ABSTRACT

Objective. A retrospective analysis was carried out to evaluate the prognostic significance of peritoneal cytology in cervical adenocarcinoma.

Methods. The records of 107 patients with FIGO stage IB to IIB cervical adenocarcinoma who underwent hysterectomy were reviewed.

Results. Sixteen patients (15%) had positive peritoneal cytology. The 5-year survival rate among patients with positive or negative cytology was 50% or 87%, respectively, showing a significant difference (log-rank, $P<0.001$). The recurrence-free survival (RFS) rate at 36 months in the cytology-positive or –negative group was 53% or 87%, respectively, the difference being significant (log-rank, $P=<0.001$). Cox model analysis revealed positive cytology [hazards ratio (HR) 6.27, 95% confidence interval (CI) 2.13–18.41], positive lymph node (HR 6.20, 95% CI 1.87–20.57), ovarian metastasis (HR 5.20, 95% CI 1.18-22.82), and histological grade (HR 5.97, 95% CI 2.00-17.78) to be independent adverse risk factors for survival among the factors analyzed (lymph node status, lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade). Cox model analysis showed that positive cytology (HR 4.58, 95% CI 1.48–14.16), positive lymph node (HR 7.61, 95% CI 2.69–21.54), and histological grade (HR6.13, 95% CI 2.14–17.77) were independent adverse risk factors for RFS. The incidence of peritoneal spread at the first recurrence among the cytology-positive group (62.5%) was significantly higher than that among the cytology-negative group (12.5%) (Fisher's exact test, $P=0.021$).

Conclusion. The presence of positive peritoneal cytology appears to be an independent prognostic risk factor in patients with cervical adenocarcinoma.

Introduction

The prognostic value of peritoneal cytology in ovarian carcinoma among gynecological malignancies is widely accepted, and it is included in the International Federation of Gynecology and Obstetrics (FIGO) nomenclature (1994) [1]. Although positive peritoneal cytology is included in the FIGO staging system for endometrial carcinoma (1988) [1], there is controversy regarding the significance of positive peritoneal cytology and there are conflicting reports in the literature [2]. As for cervical carcinoma, several reports on the significance of peritoneal cytology have been published [3–14]. Among patients with squamous cell carcinoma, the incidence of positive peritoneal cytology in FIGO stage I or II disease is low (0.3–1.8%), and it is considered that peritoneal cytology is of little value in treatment planning [3,4,10]. On the other hand, most of the remaining 10% of cervical carcinoma cases have adenocarcinoma lesions [1], and few reports on the prognostic value of peritoneal cytology in patients with cervical adenocarcinoma have been published, because of the potential limitation of small cohorts of patients. The question of the prognostic value of peritoneal cytology in cervical adenocarcinoma remains unanswered. The present retrospective study was undertaken to clarify the prognostic significance of peritoneal cytology in surgically treated patients with FIGO stage IB to IIB cervical adenocarcinoma.

Materials and methods

Patients

We reviewed the medical records and pathological materials that had been obtained from 1182 patients with FIGO stage IB-IVA invasive carcinoma of the uterine cervix, who were treated at the Gynecology

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doi:10.1016/j.ygyno.2009.08.020

Division of the National Cancer Center Hospital, Tokyo, Japan, between 1984 and 2003. This study included patients who met the following criteria: the patient had primary invasive adenocarcinoma that originated from the uterine cervix; the patient had FIGO stage IB, IIA, or IIB disease; the patient underwent abdominal hysterectomy; the peritoneal cytology was determined in a peritoneal washing obtained by laparotomy immediately upon entering the peritoneal cavity during primary surgery; and the patient had no macroscopic extrauterine disease disseminating over the surface of the peritoneum or organs in the abdominal cavity at the primary surgery. Patients with microscopic peritoneal dissemination in the abdominal cavity that was proven by pathological analysis of the resected samples were also excluded. Patients with a tumor that directly extended to the abdominal cavity through the myometrium, or a tumor that disseminated over the surface of the adnexa were excluded. Patients who received adjuvant therapy before primary surgery were excluded. Patients with squamous cell carcinoma or other epithelial tumors including adenosquamous carcinoma were excluded. Those who had other simultaneous primary malignancy including endometrial cancer, ovarian cancer, or tubal cancer were also excluded.

All of the patients were staged according to the FIGO (1994) staging system [1]. Patients treated before 1994 were restaged retrospectively on the basis of their clinical records and pathological materials. Postoperative pathological classification was performed according to the International Union Against Cancer (UICC) TNM classification of malignant tumors [15]. Histological typing was evaluated according to the criteria of the World Health Organization International Histological Classification of Tumors [16].

Cytopathology

Cytopathological diagnosis was performed according to the following procedure [2]. Cytological specimens were obtained by laparotomy immediately upon entering the peritoneal cavity. Approximately 30 ml of sterile saline was instilled into the pelvis over the uterus, and then aspirated in the cul-de-sac. When a sufficient amount of ascites was present, the fluid was removed with a 20- to 30-ml syringe. The samples were subjected to cytocentrifugation onto slide glasses at 1400 rpm at room temperature for 60 s. The slides were then fixed in 95% ethanol, followed by Papanicolau stain and Alcian blue stain. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010, Tokyo, Japan), and also for epithelial antigen using an antibody against BerEP4 (DAKOPATTS, Glostrup, Denmark). Two to three cytotechnologists and cytopathologists independently examined all of the slides to make a consensus diagnosis. A patient was considered to have positive peritoneal cytology if adenocarcinoma cells were detected regardless of the number of cancer cells. In cases where atypical cells were present but they could not be definitively identified as cancer cells, the peritoneal cytology was considered to be negative in this study.

Treatment

Our standard surgical procedure for FIGO stage IB–IIB adenocarcinoma of the uterine cervix was abdominal radical hysterectomy with bilateral salpingoophorectomy and pelvic lymphadenectomy. If a paraaortic node was found to be enlarged at the surgery, sampling for pathological examination was performed. In patients with pelvic lymph node metastasis (pT1bN1, pT2aN1, or pT2bN1) or parametrial involvement (pT2b) proven by pathological examination following surgery, adjuvant postoperative irradiation to the whole pelvis was administered. A daily dose of 2 Gy, 5 fractions a week, was given using a linear accelerator. The total dose for the whole pelvis was 50 Gy with an opposed anterior and posterior field, or a 4-field anterior–posterior and lateral technique. Following the primary treatment, asymptomatic patients underwent pelvic examination, Pap smear, chest radiograph, and determination of serial tumor markers every 4–6 months. Symptomatic patients underwent appropriate examinations where indicated by ultrasonography, computed tomography and/or magnetic resonance imaging.

Statistical methods

Survival and recurrence-free survival (RFS) curves were obtained by the Kaplan–Meier method and the survival curves were compared by nonparametric survival analysis (log-rank test). Patients were followed up through December 2007 for survival and RFS analyses. A P-value of <0.05 was considered to indicate statistical significance. Variables that showed a significant association with survival were included in multivariate analysis based on the Cox proportional-hazard model with a stepwise method (forward selection). A P-value of <0.05 was adopted as inclusion criteria, and a P-value of >0.10 was adopted as exclusion criteria for the forward selection. Fisher's exact test or Chi-square test was used to examine the differences in distribution for categorical variables, and independent sample t-test was used for statistical analysis of continuous variables. A P-value of <0.05 was considered to indicate statistical significance. Patients who died of other causes were included as deaths in the survival analysis. All statistical analyses were performed with the statistical software package SPSS for Windows (version 11.0J; SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics

A total of 161 patients with adenocarcinoma lesion in the uterine cervix of FIGO stage IB to IIB disease were treated during the study period. Of these 161 patients, 54 patients were excluded from the present study for the following reasons: 8 patients received primary radiotherapy, 1 patient had a lesion that involved the surface of the rectum at laparotomy, and 45 patients had no sample of peritoneal cytology. Of these 45 patients with no cytological samples, 1 patient had a tumor that disseminated to the mesosalpinx. The remaining 107 patients met the study criteria. The 107 patients were followed for 1 to 281 months, including until death, and the median follow-up period was 72 months. No patient was lost to follow-up.

Of the 107 patients, 16 patients (15%) had positive peritoneal cytology and 91 (85%) had negative cytology. The characteristics of the patients and tumors are shown in Table 1. The positive cytology rate was 15% (13/89) among those with FIGO stage IB disease, 50% (1/2) among those with stage IIA disease, and 13% (2/16) among those with stage IIB disease. The positive cytology rate among those with pT1b1 disease, pT1b2 disease, pT2a disease or pT2b disease was 7% (5/68), 31% (5/16), 22% (2/9), or 29% (4/14), respectively. In the positive cytology group, no enlarged paraaortic lymph node was found at laparotomy in any patient, and common iliac node metastasis was found in 3 patients (18.8%, 3/16). In the negative cytology group, paraaortic lymph node metastasis was proven pathologically in 1 patient, and common iliac node metastasis was found in 5 patients (5.5%, 5/91). One patient in the positive cytology group had clear cell carcinoma and one patient in the negative cytology group had mesonephritic adenocarcinoma; however, we did not determine the histological grade of clear cell carcinoma and mesonephritic adenocarcinoma in the present study because the role of the histological grade of these tumors has not been confirmed and is still controversial. Of these 2 patients, the patient with clear cell carcinoma suffered recurrence in the lung and died of the disease. The patient with mesonephritic tumor suffered recurrence in the vagina, and she was alive with disease after receiving salvage chemotherapy at 62 months. Eight patients (7%, 8/107) with pT1b1 disease in the negative cytology group underwent extrafascial simple hysterectomy without

Table 1
Characteristics of the patients with cervical adenocarcinoma.

		Positive peritoneal cytology $n=16$	Negative peritoneal cytology $n=91$	*P*-value
Median age (years)		48 (range, 30–66)	48 (range, 29–70)	0.811
FIGO stage	IB	13 (81%)	76 (84%)	0.365
	IIA	1 (6%)	1 (1%)	
	IIB	2 (13%)	14 (15%)	
Pathological stage	pT1b	10 (62%)	74 (81%)	0.031
	pT1b1	5 (31%)	63 (69%)	
	pT1b2	5 (31%)	11 (12%)	
	pT2a	2 (13%)	7 (8%)	
	pT2b	4 (25%)	10 (11%)	
Number of positive pelvic lymph nodes	None	11 (69%)	68 (75%)	0.072
	1–4	2 (12%)	14 (15%)	
	≧5	3 (19%)	3 (3%)	
	Not resected	0	6 (7%)	
Lymph-vascular space invasion	Negative	4 (25%)	42 (46%)	0.171
	Positive	12 (75%)	49 (54%)	
Tumor size (mm)	≤40	6 (38%)	67 (74%)	0.008
	>40	10 (62%)	24 (26%)	
Depth in cervical wall	<1/3	3 (19%)	29 (32%)	0.541
	1/3–2/3	5 (31%)	21 (23%)	
	>2/3	8 (50%)	41 (45%)	
Pathological parametrial involvement	Negative	12 (75%)	73 (80%)	0.174
	Positive	4 (25%)	10 (11%)	
	Not resected	0	8 (9%)	
Infiltration to vagina	No	11 (69%)	77 (85%)	0.155
	Yes	5 (31%)	14 (15%)	
Ovarian metastasis	Negative	14 (88%)	89 (98%)	0.105
	Positive	2 (12%)	2 (2%)	
Histological subtype	Mucinous	8 (50%)	57 (63%)	0.026
	Endometrioid	5 (31%)	31 (34%)	
	Serous	2 (13%)	1 (1%)	
	Clear cell	1 (6%)	0	
	Mesonephritic	0	1 (1%)	
	Undifferentiated	0	1 (1%)	
Histological grade	Well differentiated	10 (63%)	66 (73%)	0.511
	Moderately differentiated	3 (19%)	13 (14%)	
	Poorly differentiated	2 (12%)	11 (12%)	
	Unclassified	1 (6%)	1 (1%)	
Surgery	Radical hysterectomy	16 (100%)	83 (91%)	0.603
	Simple hysterectomy	0	8 (9%)	
Surgical margin	Free	15 (94%)	91 (100%)	0.150
	Close	1 (6%)	0	
Postoperative therapy	Not done	11 (69%)	71 (78%)	0.044
	Radiotherapy	2 (12%)	17 (19%)	
	Chemotherapy	3 (19%)	3 (3%)	

systemic pelvic lymphadenectomy for the following reasons: 3 patients were elderly patients over 69 years of age, and 5 patients had a lesion of small volume and well-differentiated histological grade. Of these 8 patients, 1 elderly patient with moderately differentiated endocervical-type adenocarcinoma developed recurrence in the lung and died of the disease. While the tumors were completely removed in all cases, the vaginal surgical cut margin of one patient with positive cytology was close microscopically (<5 mm). This patient developed recurrence in the bone and died of the disease. Six patients (6%, 6/107) received postoperative adjuvant chemotherapy, while our standard adjuvant therapy was radiotherapy. The reasons for administration of chemotherapy were vesicovaginal fistula following surgery in 1 patient, and personal agreement between the patient and her physician at that time in the remaining 5 patients.

Survival

The cumulative survival was assessed in subgroups according to peritoneal cytology (negative or positive), number of positive nodes (none, 1–4, ≥5, or not resected), lymph-vascular space invasion (negative or positive), tumor size (≤40 mm or >40 mm), depth in cervical wall (<1/3, 1/3–2/3, or >2/3), pathological parametrial involvement (negative, positive or not resected), infiltration to vagina (no or yes), ovarian metastasis (negative or positive), histological subtype (mucinous, endometrioid, or other rare types), and histological grade (well, moderately, poorly differentiated, or unclassified). The 5-year survival rate was 50% [95% confidence interval (95% CI), 38–63%] among the positive cytology group and 87% (95% CI, 83–90%) among the negative cytology group, showing a significant difference (log-rank, $P<0.001$). Significant differences in survival were also found among the patients in subgroups according to the number of positive nodes, lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis and histological grade (Table 2). Multivariate analysis of testing for differences in survival among these 9 significant variables was performed. The Cox model revealed that positive cytology, lymph node status, histological grade, and ovarian metastasis were independent adverse risk factors for survival (Table 3).

Similarly, the RFS was assessed in the same subgroups. The RFS at 36 months was 53% (95% CI, 40–66%) among the positive cytology group and 87% (95% CI, 83–90%) among the negative cytology group, the difference being significant (log-rank, $P=0.0005$). Univariate analysis also revealed significant differences in the RFS of patients in subgroups according to the number of positive nodes (log-rank, $P<0.001$), lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade (Table 2). Among these 9 significant variables, the Cox model showed that positive cytology, lymph node status, and histological grade were independent adverse risk factors (Table 4).

Spread pattern and failure sites

Eight patients (50%, 8/16) in the positive cytology group and 16 patients (22%, 16/91) in the negative cytology group suffered tumor recurrence. As to the distribution of the first recurrent site, among the 8 patients with positive cytology who recurred, the most frequent first recurrent site was peritoneal spread (62.5%, 5/8), followed by the lung (12.5%, 1/8), bone (12.5%, 1/8), and pelvis (12.5%, 1/8). Among the 16 patients with negative cytology who recurred, the most frequent first recurrent sites were the pelvis (27.8%, 5/18), lung (27.8%, 5/18), and distant node (27.8%, 5/18) followed by peritoneal spread (11.1%, 2/18) and liver (5.5%, 1/18). The incidence of peritoneal spread in the recurrent patients with positive cytology (62.5%, 5/8) was significantly higher than that in the recurrent patients with negative cytology (12.5%, 2/16) (Fisher's exact test, $P=0.021$).

Discussion

In the present study, we found that the presence of positive peritoneal cytology is an independent adverse prognostic risk factor in surgically treated patients with FIGO stage IB to IIB cervical adenocarcinoma who had no apparent peritoneal spread at the initial surgery, and that it seems to reflect the potential of developing to peritoneal spread. Since 1980, there have been several reports concerning the peritoneal cytology of patients with cervical adenocarcinoma [4,5,8,9,11,12,14]. In these previous reports, the incidence of positive peritoneal cytology was 0% to 20%. Most of these studies included various stages (stage I to IV), treatment modalities, or clinical status (primary or recurrent disease). Also, the number of enrolled patients was small (range, 6–69, median, 18). As for prognostic evaluation, patients with adenocarcinoma were analyzed together with patients with squamous cell carcinoma,