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SPECIAL ARTICLE

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Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus

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V. Preoperative adjuvant therapy

• Summary

Preoperative chemotherapy: there have been three reports of meta-analyses based on randomized controlled trials carried out in Europe or North America that compared surgical resection with preoperative chemotherapy and surgical resection alone. However, the conclusions are conflicting: one found that preoperative chemotherapy does not improve 1-year and 2-year survival rates, whereas the other showed preoperative chemotherapy to slightly improve the 2-year survival rate. At present, the efficacy of preoperative chemotherapy for resectable cases (T1–3, N0,1, M0; 2002 edition of UICC classification) is unclear.

Preoperative chemoradiotherapy: the results of a meta-analysis of randomized controlled trials comparing surgery alone and surgery combined with preoperative chemoradiotherapy carried out in Europe and North America showed that preoperative concurrent chemoradiotherapy (20–45 Gy) for resectable cases (T1–3, N0,1, M0) caused a significant increase in operation-related mortality while significantly improving the 3-year survival rate. However, when the 1-year or 2-year survival rate was the endpoint, there was no clear survival benefit of preoperative chemoradiotherapy. Thus, the results of this meta-analysis of randomized controlled trials performed in Europe and North America suggest that preoperative chemoradiotherapy combined with surgery has the potential to improve the long-term survival of patients undergoing surgical resection of esophageal carcinoma. In Japan, this therapy is performed for locally advanced cases in a number of institutions. However, no high-level evidence is available concerning Japanese patients, and there is no firm basis for recommending the use of preoperative chemoradiotherapy in Japan.

The rationale for preoperative adjuvant therapy is the expectation that it will regress the primary lesion, control lymph node metastasis and micrometastasis, and allow downstaging before surgical resection, leading to better long-term results of the surgery. Besides downstaging, preoperative adjuvant therapy is also advantageous in that it allows tests of sensitivity to chemotherapy and radiotherapy by histological investigation of the resected specimen. On the other hand, preoperative adjuvant therapy has the following

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drawbacks: drug resistance may be induced; local control is delayed, and metastatic spread is facilitated in ineffective cases, surgical manipulations are more difficult, and the risk of postoperative complications may increase in patients having undergone preoperative radiotherapy.

In Europe and North America, surgery plus preoperative adjuvant therapy has been extensively compared with surgery alone in randomized controlled trials. However, the histological type of esophageal carcinomas subjected to these studies was mostly adenocarcinoma rather than squamous cell carcinoma, and the surgical procedures included not only resection and dissection via thoracotomy but also transhiatal esophagectomy. Therefore, prudence is required when interpreting the results of these controlled trials.

1. Preoperative chemotherapy (neoadjuvant chemotherapy)

The effects of neoadjuvant chemotherapy on patient survival have often been studied in Europe and North America. Representative randomized controlled trials are described below.

In a large-scale randomized controlled trial in the United States (comparison between 213 patients treated by three courses of 5-FU/cisplatine neoadjuvant chemotherapy and surgery and 227 patients treated by surgery alone), there was no significant difference in overall survival or disease-free survival between the two groups. In this study, 54% of the subjects had adenocarcinoma. On the other hand, a large-scale randomized controlled trial in the UK (comparison of 400 patients who underwent two courses of 5-FU/cisplatine neoadjuvant chemotherapy plus surgery and 402 patients who underwent surgery alone) showed significantly better results for the neoadjuvant chemotherapy group, with a median survival period of 16.8 months versus 13.3 months and a 2-year survival rate of 43% versus 34%. Patients with adenocarcinoma accounted for 66% in this study. Thus, even with large-scale randomized controlled trials including more than 200 patients per group, the results are contradictory as to the efficacy of neoadjuvant chemotherapy. In a randomized controlled trial covering esophageal squamous cell carcinoma (comparison of 74 patients who underwent two courses of 5-FU/cisplatine neoadjuvant chemotherapy plus surgery and 73 patients who underwent surgery alone), neoadjuvant chemotherapy caused downstaging but achieved no significant difference in survival.

There are three reports of meta-analysis based on overseas randomized controlled trials that compared neoadjuvant chemotherapy plus resection and resection alone. A meta-analysis based on six randomized controlled trials, and targeting a 1-year survival rate as the endpoint, revealed no significant difference in the survival rate. On the other hand, a meta-analysis based on seven randomized controlled trials and targeting a 2-year survival rate as the endpoint showed a 4.4% increase in the survival rate after neoadjuvant chemotherapy ($P = 0.07$). When only the four recent randomized controlled trials using chemotherapy with 5-FU/cisplatine were considered, the 2-year survival rate was found to be increased by 6.3%. However, another meta-analysis using the 2-year survival rate as the endpoint revealed no survival increase after chemotherapy. Accordingly, the efficacy of neoadjuvant chemotherapy for resectable carcinoma (T1-3, N0,1, M0; 2002 edition of UICC classification) is unclear.

2. Preoperative chemoradiotherapy (neoadjuvant chemoradiotherapy)

Neoadjuvant chemoradiotherapy has been employed aggressively since the late 1980s in Europe and North America. There have been several randomized controlled trials that verified the beneficial effect of neoadjuvant chemoradiotherapy on patient survival. In Japan, a number of institutions currently use neoadjuvant chemoradiotherapy in patients with locally advanced carcinoma. However, sufficient high-level evidence as to the effectiveness of neoadjuvant chemoradiotherapy in Japanese patients is lacking. An outline of the results of representative randomized controlled trials focusing on this issue, performed in Europe and North America, is presented next.

In a randomized controlled trial carried out by the Michigan group in the United States (comparison between 50 patients given neoadjuvant 5-FU/cisplatin/vinblastine + acceler-

ated hyperfractionated radiation 45 Gy/30 times/3 weeks with surgery and 50 patients who underwent transhiatal esophagectomy alone; 75% had adenocarcinomas), no significant difference in the overall survival rate or disease-free survival rate was found between the two groups examined. On the other hand, in a randomized controlled trial carried out in patients with esophageal adenocarcinoma in Ireland (comparison between 55 patients treated by two courses of neoadjuvant 5-FU/cisplatin + accelerated radiation 40 Gy/15 times/3 weeks with surgery and 58 patients treated by surgery alone), there was a significant difference in the 3-year survival rate between the two groups. However, because the 3-year survival rate in patients treated by surgery alone was extremely low at 6%, the validity of the treatment cannot be verified. In a controlled trial in patients with squamous cell carcinoma carried out in France (comparison between 143 patients treated by two courses of neoadjuvant cisplatin + split-course radiation 37 Gy/10 times/4 weeks with surgery and 139 patients treated by surgery alone), neoadjuvant chemoradiotherapy did not prolong survival, but significantly improved the disease-free survival period. Several other randomized controlled trials have demonstrated definite prolongation of the survival period in patients who responded to neoadjuvant chemoradiotherapy, although there was no significant intergroup difference in the overall survival rate.

There are five reports of meta-analyses that compared resection with and without neoadjuvant chemoradiotherapy. All these meta-analyses were based on five to seven randomized controlled trials carried out in Europe or North America that compared surgery with and without neoadjuvant chemoradiotherapy in patients with resectable carcinoma not accompanied by distant metastasis. The results of meta-analyses using the 1-year or 2-year survival rate as the endpoint showed no beneficial effect of neoadjuvant chemoradiotherapy on the survival rate. On the other hand, two meta-analyses using the 3-year survival rate as the endpoint showed that neoadjuvant chemoradiotherapy (20–45 Gy) in resectable cases decreased the local recurrence rate and significantly increased the 3-year survival rate while significantly increasing operation-related mortality within 90 days. A meta-analysis using the hazard ratio of the survival curve as the endpoint showed a 14% decrease in death score attributable to neoadjuvant chemoradiotherapy ($P = 0.07$). Of the six randomized controlled trials included in this meta-analysis, five showed a higher, but not significantly so, survival rate for patients given neoadjuvant chemoradiotherapy, whereas the other randomized trial that examined esophageal adenocarcinoma showed a significant increase in the survival rate in patients given neoadjuvant chemoradiotherapy. On the other hand, an Australian randomized controlled trial reported in 2005 (comparison between 128 patients treated by neoadjuvant 5-FU/cisplatin + radiotherapy 35 Gy/15 times/3 weeks with surgery and 128 patients treated by surgery alone; 62% had adenocarcinomas) showed no significant difference in overall survival between the two groups, but the disease-free survival rate was significantly higher in the neoadjuvant chemoradiotherapy group patients with squamous cell carcinoma. Thus, there was not necessarily a consistent difference according to the histological type.

Thus, according to the results of meta-analyses based on data from Europe and North America, neoadjuvant chemoradiotherapy is a combination therapy that can improve long-term survival after 3 years in patients with resectable carcinomas (T1–3, N0,1, M0; 2002 edition of UICC classification). However, no randomized controlled trials of neoadjuvant chemoradiotherapy have been carried out in Japan. Thus, there is no sufficient evidence for recommending this therapy as an effective preoperative therapy.

VI. Postoperative adjuvant therapy

- Summary

Postoperative chemotherapy: a randomized controlled trial that compared surgery with and without postoperative chemotherapy (5-FU/cisplatin, two courses) in Japan demonstrated that postoperative chemotherapy caused a significant increase in the disease-free survival rate in patients given postoperative chemotherapy as compared with those who underwent surgery alone, but that there was no significant difference in the overall

survival rate. Similar randomized controlled trials carried out in Europe or North America confirmed the lack of a difference between the two groups. Thus, there is insufficient evidence to assume a benefit of postoperative chemotherapy for increasing the overall survival rate of patients undergoing curative resection. However, considering that the disease-free survival rate increased significantly in the randomized controlled trial carried out in Japan, the recurrence-preventive effect of postoperative chemotherapy is apparent. If the evidence obtained in this country is regarded as important, postoperative chemotherapy seems effective for preventing postoperative recurrence.

Postoperative radiotherapy: the results of a randomized controlled trial of pre- and postoperative radiotherapy versus postoperative radiotherapy alone, carried out by the Japan Clinical Oncology Group (JCOG) esophageal oncology group, showed that the overall survival rate was significantly higher in patients given postoperative radiotherapy alone when attention was focused on the eligible patients who underwent treatment according to the protocol. Based on this, preventive postoperative irradiation was once in widespread use in Japan. On the other hand, in overseas randomized controlled trials that compared surgery with and without postoperative irradiation (usual fractionation, 45–60 Gy), postoperative irradiation decreased local recurrence in the irradiated field but did not significantly increase the survival rate. Therefore, there is little evidence for recommending postoperative irradiation after curative resection as a standard treatment. At present, the significance of postoperative chemoradiotherapy is unclear. In clinical practice for patients undergoing noncurative resection or postoperative local recurrence, chemoradiotherapy has been employed, and its efficacy has also been reported. Although sufficient evidence is lacking, some local therapy is necessary for patients who have undergone noncurative resection and who have macroscopic residual tumor without distant metastasis. Chemoradiotherapy seems to be a useful treatment option for such patients.

The rationale for implementing postoperative adjuvant therapy is the potential of this therapy to control local residual tumor after surgical resection, metastasis to lymph nodes, or distant micrometastasis, leading to improved long-term results. The advantage of postoperative adjuvant therapy is that it is possible to implement treatment suitable for the disease stage accurately determined by surgery. On the other hand, its disadvantage is that the absence of evaluable lesions makes it difficult to determine the efficacy of postoperative adjuvant therapy. Although preoperative adjuvant therapy is the mainstream in Europe and North America, radical resection followed by postoperative chemotherapy is most common in Japan, where treatment of esophageal carcinoma has been led by surgeons.

1. Adjuvant chemotherapy

In a randomized controlled trial in patients with squamous cell carcinoma carried out by the Japan Clinical Oncology Group (JCOG)/Esophageal Oncology Group (comparison between 105 patients treated by surgery with two courses of postoperative cisplatin/vindesine and 100 patients treated by surgery alone), postoperative chemotherapy added no survival benefit; i.e., there was no significant difference in 5-year survival rates. Thereafter, another randomized controlled trial using chemotherapy with 5-FU/cisplatin for esophageal squamous cell carcinoma (JCOG9204: comparison between 122 patients treated by surgery with two courses of postoperative 5-FU/cisplatin and 120 patients treated by surgery alone) showed no clear intergroup difference in the overall survival rate. The disease-free survival period was, however, longer in patients given postoperative chemotherapy than in those treated by surgery alone, with the disease-free survival rate being 58% for the former and 43% for the latter, showing the recurrence-preventive effect of postoperative chemotherapy. In particular, the recurrence-preventive effect was suggested in patients with positive lymph nodes, whereas no such effect was noted in those with negative lymph nodes. In a randomized controlled trial carried out in France (comparison between 52 patients treated by surgery with six to eight courses of postoperative 5-FU/

cisplatin and 68 patients treated by surgery alone), approximately half the subjects underwent palliative resection. The median survival period was 14 months in both groups of patients, and the researchers concluded that postoperative chemotherapy with 5-FU/cisplatin was not effective. A meta-analysis based on these randomized controlled trials also showed no beneficial effect of adjuvant chemotherapy on the overall survival rate.

Thus, there is no evidence showing that adjuvant chemotherapy improves the survival rate of patients undergoing curative resection. However, a Japanese randomized study (JCOG9204) achieved a significant increase in the disease-free survival rate after adjuvant chemotherapy, showing the recurrence-preventive effect of this therapy. Considering that the accuracy of lymph node dissection is high in Japan, and putting weight on the evidence obtained in this country, adjuvant chemotherapy (5-FU/cisplatin, two courses) appears to have a role in prevention of postoperative recurrence.

2. Adjuvant radiotherapy

Preoperative irradiation used to be a standard treatment. However, because there was no documentation that preoperative irradiation improved the survival rate, the JCOG Esophageal Oncology Group performed a randomized controlled trial in 1981–1984 to compare preoperative (30 Gy/15 times) plus postoperative (24 Gy/12 times) irradiation and postoperative irradiation alone (50 Gy/25 times). As this study included a number of cases excluded from analysis because of noncurative resection or surgical complications, it is slightly less reliable. However, the overall survival rate of eligible patients who underwent the protocol treatment was significantly higher in those given postoperative irradiation alone. Based on this finding, prophylactic postoperative irradiation came into common use.

On the other hand, four overseas randomized controlled trials comparing surgery with and without postoperative irradiation (usual fractionation, 45–60 Gy) demonstrated no significant increase in the survival rate, although local recurrence in the irradiated field was decreased by postoperative irradiation. A meta-analysis based on these controlled trials also showed no increase in the survival rate after postoperative irradiation. Therefore, there is little evidence for recommending postoperative radiotherapy following curative resection as a standard treatment. However, a subset analysis of a large-scale randomized controlled trial including a total of 495 patients in China showed that postoperative radiotherapy caused a significant increase in the survival rate for stage III patients. Therefore, postoperative radiotherapy may be of clinical value for selected patients.

VII. Chemotherapy

• Summary

Chemotherapy in the treatment of esophageal carcinoma is usually combined with surgery or radiotherapy in the form of preoperative or postoperative adjuvant chemotherapy or chemoradiotherapy. The use of chemotherapy not combined with other modalities is limited to patients with distant metastasis (M1b) or postoperative distant recurrence. Currently, 5-FU + cisplatin is the most common combination regimen for chemotherapy. However, there is no definite evidence for prolongation of the survival period, and this therapy is thus regarded as a palliative treatment.

1. Monotherapy drugs active for esophageal cancer

Many chemotherapy drugs, such as 5-FU, cisplatin, mitomycin C, bleomycin, vindesine, adriamycin, paclitaxel, docetaxel, vinorelbine, nedaplatin, irinotecan, and gemcitabine, are known to be effective for esophageal carcinoma (Table 3). However, only 15%–30% of patients respond to monotherapy, including rare cases showing a complete

Table 3. Efficacy of monochemotherapy for carcinoma of the esophagus (approved agents in Japan)

Drug	Dose and schedule	No. of cases	Response rate (%)
5-FU	500 mg/m^2/day × 5 days	26	15
Mitomycin-C	20 mg/m^2 every 4–6 weeks	24	42
Cisplatin	50 mg/m^2 every 3 weeks	24	25
Vindesine	3–4.5 mg/m^2 every week	23	18
Docetaxel	70 mg/m^2 every 3 weeks	48	21
Nedaplatin	100 mg/m^2 every 4 weeks	29	52

Table 4. Efficacy of major combination therapies

Drug	Histological type	No. of cases	Response rate (%)
Cisplatin + 5-FU	Squamous cell carcinoma	39	36
Cisplatin + Paclitaxel*	Squamous cell carcinoma/ adenocarcinoma	32	44
Cisplatin + Irinotecan*	Squamous cell carcinoma/ adenocarcinoma	35	57
Cisplatin + Gemcitabine*	Squamous cell carcinoma/ adenocarcinoma	32	45
Nedaplatin + 5-FU	Squamous cell carcinoma	38	40

*Not approved agents in Japan (as of October 2006)

response (CR), and no survival prolongation has been demonstrated with monotherapy. At present, the most commonly used drugs are 5-FU and cisplatin. Basic research has demonstrated that these two drugs are effective as monotherapy and exert a synergetic effect when combined with other therapy or a sensitizing effect when combined with radiotherapy. It has also occasionally been reported that these drugs achieve good results as combination therapy in the clinical setting. These are the reasons for the widespread use of these two drugs. As of October 2006, the use of paclitaxel, vinorelbine, irinotecan, and gemcitabine for the treatment of esophageal carcinoma has not been approved in Japan.

2. Efficacy in combination therapy

Although various combination therapies using cisplatin have been employed since the clinical introduction of this drug (Table 4), currently the most common regimen is 5-FU plus cisplatin. In other countries, this combination therapy is usually performed employing the following regimen: continuous intravenous infusion of 5-FU 1000 mg/m^2/day, for 4–5 days, plus cisplatin 100 mg/m^2 on day 1. In contrast, a phase II clinical trial carried out in Japan showed a response rate of 36% to the regimen of 5-day continuous IV infusion of 5-FU 700 mg/m^2/day plus cisplatin 70 mg/m^2 on day 1. A report comparing this combination therapy and the best supportive care was published overseas and demonstrated no definite prolongation of survival. However, this combination therapy was used mainly as postoperative adjuvant chemotherapy for patients after curative resection, and those with distant metastasis were rare. Therefore, the effect of this combination therapy on survival remains unclear. Although in recent years regimens using paclitaxel, irinotecan, or gemcitabine have been tried overseas, while regimens using nedaplatin have been tried in Japan, these regimens have not been studied in large-scale phase III trials. Thus, whether the merits of these regimens surpass those of the standard combination of 5-FU + cisplatin have yet to be demonstrated. Currently in Japan, the combination of 5-FU + cisplatin is commonly used as a primary treatment, followed by docetaxel as a secondary treatment. In any event, the use of chemotherapy alone, regardless of whether it is combination therapy or monotherapy, has limitations, and chemotherapy not combined with other treatment modalities is applied only to patients with unresectable metastatic lesions.

VIII. Radiotherapy

• Summary

As compared with radiation monotherapy, concurrent chemoradiotherapy significantly increases the survival rate whereas radiotherapy after induction chemotherapy does not. Concurrent chemoradiotherapy is indicated for patients with resectable T1–3, N0,1, M0 carcinoma (UICC-TNM classification, 2002 edition), if they are in good general condition. This type of chemoradiotherapy can also be applied to patients with unresectable locally advanced carcinoma (T4, N0,1, M0) or those with advanced carcinoma accompanied by metastasis to supraclavicular lymph nodes (M1/LYM), but the risk of serious complications including fistulation increases. In definitive radiation monotherapy, irradiation of 60–70 Gy/30–35 times/6–7 weeks delivered by conventional fractionation is necessary. In definitive concurrent chemoradiotherapy, radiation of at least 50 Gy/25 times/5 weeks by conventional fractionation is necessary. Although 50 Gy is the standard dose of concurrent chemoradiotherapy in the Unites States, irradiation to approximately 60 Gy is employed in concurrent chemoradiotherapy in Japan.

According to a Chinese randomized controlled trial, late accelerated hyperfractionated radiation, which allows the total duration of irradiation to be reduced, achieves a significantly higher survival rate than conventional fractionated radiation, and is comparable to concurrent chemoradiotherapy. Therefore, accelerated hyperfractionated radiation is a useful therapy for patients with squamous cell carcinoma in whom the use of combined chemotherapy is difficult. Because prolongation of the duration of irradiation decreases the local control rate of radiation monotherapy, it is recommended to avoid rest periods of radiation therapy.

A Japanese randomized controlled trial revealed that combined use of external beam radiation and intracavitary radiation is effective for patients with T1–2 esophageal carcinoma at a relatively early stage. However, chemoradiotherapy has been widely used, and sufficient evidence to recommend adding intracavitary radiation to chemoradiotherapy is lacking.

Radiotherapy was primarily used for patients not indicated for surgery or endoscopic mucosal resection (EMR). However, in recent years, radiotherapy (particularly, chemoradiotherapy) has been widely used for both superficial carcinoma and locally advanced carcinoma as a definitive treatment.

The standard radiotherapy for esophageal carcinoma is mentioned in accordance with the Report of the Committee for Standardizing Irradiation, Report of the Study Group for Standardization of Radiotherapy for Superficial Carcinoma of the Esophagus (Japanese Society for Therapeutic Radiology and Oncology), and the Radiotherapy Planning Guidelines 2004 (edited by Japanese College of Radiology, Japanese Society for Therapeutic Radiology and Oncology, and Japan Radiological Society). Key points are described next.

1. Definitive radiotherapy

(1) Indications

Definitive radiotherapy is used when control of all lesions, leading to a cure, is expected. Definitive irradiation is best suited for resectable cases with T1–3, N0,1, M0 carcinoma (UICC-TNM classification, 2002 edition). Unresectable cases with T4, N0,1, M0 carcinoma and advanced cases with metastasis to supraclavicular lymph nodes are also candidates for this therapy. When the general condition is favorable, allowing combined use of chemotherapy, the standard treatment is chemoradiotherapy, rather than radiation alone.

(2) Target volumes

Gross tumor volume (GTV): the primary tumors detected by endoscopy and esophageal barium contrast study as well as metastatic regional lymph nodes (N1), if any, are included in the GTV. In esophageal carcinoma, it is difficult to determine the presence of lymph node metastasis on the basis of tumor size. However, there is a report that lymph nodes measuring 5 mm or more as determined by CT or MRI should be treated by radiotherapy, regarding the nodes as metastatic foci.

Clinical target volume 1 (CTV1): CTV1 is defined as the entire circumference of the esophagus including the GTV on endoscopy or esophageal barium study, as well as possible microscopic lesions with 2–4 cm in the cephalocaudal direction and regional lymph nodes. However, because T1a carcinomas invading the EP or LPM are not likely to have lymph node metastasis, lymph node irradiation is unnecessary. On the other hand, lymph node metastasis is present in 10%–50% of superficial lesions that are T1a-MM or SM carcinomas. Therefore, prophylactic irradiation to regional lymph nodes is required, as in advanced esophageal carcinoma. However, there is no definite consensus on the extent of lymph node areas to be irradiated as CTV. Table 5 lists standard CTV1 in relation to the site of the primary lesion. The irradiation regimen for these areas should be 40–46 Gy/20–23 times.

Clinical target volume 2 (CTV2): CTV2 is the clinical target volume after irradiation of 40–46 Gy to CTV1. CTV2 should cover microscopic lesions approximately 2 cm in the cephalocaudal direction for the entire circumferences including the GTV on endoscopy and esophageal barium study. If there is metastasis to regional lymph nodes (N1), these should also be included in CTV2. In patients receiving external radiation monotherapy, a total of up to 60–70 Gy/30–35 sessions are needed for these areas.

Planning target volume 1 (PTV1): the planning target volume at the beginning of radiotherapy (PTV1) should include CTV1 with adequate margins (0.5–1.0 cm in the side direction and 1–2 cm in the cephalocaudal direction), allowing for respiratory movement and setup errors.

Planning target volume 2 (PTV2): the planning target volume for the reduced exposure field at 40–46 Gy (PTV2) should include CTV2 with adequate margins (0.5–1.0 cm in the side direction and 1–2 cm in the cephalocaudal direction). At this time, the spinal cord should be excluded from the radiation field by the oblique opposing portal technique, etc.

Table 5. Standard lymph node regions according to the site of the primary tumors as CTV1

Cervical esophagus (Ce):
From middle deep cervical lymph nodes [102-mid] to tracheal bifurcation lymph nodes [107] (short-T-shaped radiation field)

Upper thoracic esophagus (Ut):
From supraclavicular lymph nodes [104] to middle thoracic paraesophageal lymph nodes [108] (T-shaped radiation field)

Middle thoracic esophagus (Mt):
a. FROM supraclavicular lymph nodes [104] to lower thoracic paraesophageal lymph nodes [110] or to perigastric lymph nodes (T-shaped radiation field)
b. From recurrent nerve lymph nodes [106-rec] and upper thoracic lymph nodes [105] to lower thoracic paraesophageal lymph nodes [110] (I-shaped radiation field), or to perigastric lymph nodes (L-shaped radiation field)

Lower thoracic esophagus (Lt):
From recurrent nerve lymph nodes [106-rec] and upper thoracic lymph nodes [105] to perigastric lymph nodes (cardiac lymph nodes [1,2], lesser curvature lymph nodes [3], left gastric artery lymph nodes [7]) (L-shaped radiation field)

Patients of advanced age or with complications:
Only lymph node regions around the primary tumor (local radiation field)

Note: There is no consensus on CTV1 for primary tumors originating in the middle thoracic esophagus (Mt)

(3) Treatment planning and the irradiation method

The exposure field is determined by two-dimensional planning based on X-ray simulator images or by three-dimensional planning based on CT images. If an X-ray simulator is used for positioning, the target volume should be determined under X-ray fluoroscopy, using CT findings for reference. If a superficial lesion cannot be visualized in the esophageal barium study, clipping the upper and lower parts of the lesion under endoscopy is required.

Recently, three-dimensional planning based on CT images has become common. This method allows an understanding of the three-dimensional positional relationships between the target volume and organs at risk, and is useful for implementing high-accuracy radiotherapy to minimize exposure to organs at risk.

The energy for external irradiation should be 6–15 MV. The reference dose point is the isocenter of the body thickness at the time of planning using an X-ray simulator, whereas the PTV center is used at the time of three-dimensional planning. Irradiation should be initiated with an anteroposterior opposing technique or by the fixed multiple field technique. At a dose of 44–46 Gy for radiation alone or a dose of approximately 40 Gy for chemoradiation therapy, the spinal cord should be excluded. The oblique opposing portal technique is used for thoracic or abdominal esophageal carcinomas, whereas the oblique anterior portal technique is used for cervical esophageal carcinomas.

(4) Dose fractionation and combination therapy

In general, the conventional fractionation method is used. The standard radiation dose for chemoradiotherapy in the US is 50 Gy/25–28 times/5–6 weeks. In contrast, in Japan, the standard radiation dose is about 60 Gy/30 times/6–8 weeks for chemoradiotherapy and 60–70 Gy/30–35 times/6–7 weeks for radiation monotherapy. Details of chemoradiotherapy are given in the Chemoradiotherapy section.

For superficial esophageal carcinomas, the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) research group has proposed guidelines for the standard method of radiotherapy (Table 6). In principle, treatment of SM carcinoma is considered to require an exposure dose similar to that for T2 or more advanced carcinomas. The 2-year survival rates in 141 patients with superficial carcinoma treated according to these guidelines were favorable, i.e., 90% for M carcinoma and 81% for SM carcinoma.

The total duration of irradiation is an important factor in radiotherapy for esophageal squamous cell carcinoma. The local control rate is known to decrease as the total duration of irradiation increases. Therefore, in radiation monotherapy, it is important to avoid pro-

Table 6. Guidelines for the treatment of superficial esophageal carcinoma (JASTRO Study Group)

Depth of invasion	External radiation	Intracavitary radiation	Total dose
T1a-EP to T1a-LPM			
External radiation monotherapy	60–66 Gy/30–33 times/6–6.6 weeks	–	60–66 Gy
High-dose-rate intracavitary radiation monotherapy	–	28–32 Gy/7–8 times/ twice weekly	28–32 Gy
	–	32.5–35 Gy/13–14 times/4 times weekly	35 Gy
T1a-MM to T1b-SM3			
External radiation monotherapy	60–70 Gy/usual fractionation or accelerated hyperfractionation	–	60–70 Gy
External radiation + high-dose-rate intracavitary radiation	50–60 Gy/25–30 times/5–6 weeks	8–12 Gy/3–4 times	58–72 Gy
External radiation + low-dose-rate intracavitary radiation	60 Gy/30 times/6 weeks	12 Gy/3 times	72 Gy

Table 7. Clinical results of external radiation therapy with or without intracavitary radiation for superficial esophageal carcinoma reported in Japan

Author	No. of cases	Disease stage	Local control rate		Overall survival rate	
			External radiation monotherapy	Combined intracavitary radiation	2-year	5-year
Okawa (1995)[a]	115	T1a, T1b	72%	85%	75%	39%
Akagi (1999)	35	T1a, T1b	–	74%	–	38%
Nishimura (1999)	21	T1a, T1b	45% (2 years)	85% (2 years)	–	76%
Nemoto (2000)[a]	78	T1b	66%	–	73%	45%
Nemoto (2001)[a]	95	T1b	No difference		72%	42%
Kodaira (2003)	33[b]	T1a, T1b	–	–	74%	–
Sai (2005)	34	T1a, T1b	54% (2 years)	79% (2 years)	70%	59%
Ishikawa (2005)	38	T1a, T1b	78%	90%	80%	61%
Shioyama (2005)	29[b]	T1a, T1b	No difference		81%	62%
Nemoto (2006)[a]	42[b]	T1a	No difference		90%	–
	99[b]	T1b	No difference		81%	–

T1a, mucosal carcinoma; T1b, submucosal carcinoma

[a] Reports of pooled data from multiple centers

[b] Cases with concurrent chemoradiotherapy are included; unmarked numbers indicate cases of radiation monotherapy

longation of the duration of treatment. A Chinese randomized controlled trial examined late-course accelerated hyperfractionated irradiation (68.4 Gy/41 times/6–7 weeks) consisting of twice-daily hyperfractionated irradiation in the late course of treatment to reduce the total duration of irradiation, in comparison with conventional fractionated irradiation (68.4 Gy/38 times/7–8 weeks). This study showed the survival rate to be significantly higher for the late course accelerated hyperfractionated irradiation that resulted in a 1-week-shorter duration of irradiation. Another randomized trial that compared late-course accelerated hyperfractionated irradiation with and without concurrent chemotherapy revealed a slightly lower survival rate for radiation alone, although the difference between the two groups was not statistically significant. Thus, it is presumed that hyperfractionated irradiation is a useful method of irradiation for patients in whom combined chemotherapy is difficult.

Intracavitary irradiation is basically used as a radiation boost to control the primary tumor after the end of external irradiation. In superficial esophageal carcinomas, the lesion is localized in the mucosal layer and is close to the radiation source, allowing for intracavitary irradiation to deliver a sufficient radiation dose to the tumor. Therefore, intracavitary irradiation is considered to be suitable for the treatment of superficial esophageal carcinoma. Thus, in Japan, it is commonly employed as a radiation boost following external irradiation. Table 7 lists representative trials that examined external radiation monotherapy with or without intracavitary irradiation for superficial esophageal carcinoma. A retrospective report from a single institution documented that a radiation boost by intracavitary irradiation achieved favorable therapeutic results. On the other hand, a report by Nemoto et al., who reviewed multicenter studies in Japan, indicated that there was no difference in survival rate between external radiation monotherapy and external radiotherapy combined with intracavitary irradiation. Although efficacy has not been demonstrated in randomized controlled trials focusing on superficial esophageal carcinomas, randomized controlled trials of intracavitary irradiation for esophageal carcinoma including advanced cases in Japan have shown intracavitary irradiation to be effective for esophageal carcinomas measuring 5 cm or less or T1–2 tumors. However, concurrent chemoradiotherapy is more common, and the efficacy and safety of chemoradiotherapy with an intracavitary irradiation boost are not necessarily clear. When using intracavitary irradiation, it is safer to use it after radiation monotherapy, rather than chemoradiotherapy.

For intracavitary irradiation, a balloon applicator measuring 15 mm or more in diameter should be used to avoid uneven distribution of the radiation dose. It is also recommended to use an applicator measuring 20 mm in diameter in cases with good extensibility of the esophageal wall. The point of dose assessment should be 5 mm outside to the applicator

surface (5 mm submucosal), and the dose on the mucosal surface should also be specified. Although there is no definite consensus about the optimal dose fractionation of intracavitary irradiation because of the related issue of the external irradiation dose, the general practice is that an external irradiation of 50–60 Gy is followed by intracavitary irradiation at 8–12 Gy/2–4 times (3–4 Gy on each session) (see Table 6). Because an increase in fraction size of intracavitary irradiation leads to an increased risk of late complications such as esophageal ulcers and perforation, it is recommended to perform one or two sessions of irradiation per week at a dose of 4 Gy or less for each session of high-dose-rate irradiation, or at a dose of 6 Gy or less for each session of low-dose-rate irradiation.

(5) Complications

Major early adverse events include radiation dermatitis, radiation esophagitis, and radiation pneumonia. Radiation esophagitis is almost inevitable, but the possibility of esophagomycosis or reflux esophagitis should also be borne in mind. Radiation pneumonia, which can be sometimes serious, requires differentiation from infectious disease or carcinomatous lymphangitis.

As late adverse events, esophageal perforation and bleeding occur in a few percent of patients treated by radiotherapy. The incidence of late adverse events is increased in T4 cases. When high-dose-rate irradiation is combined, special caution as to the occurrence of esophageal ulcers is necessary. Esophageal stenosis may also occur in patients with circumferential disease or those with repeated EMR. Thoracic vertebral compression fracture within the radiation field requires particular attention, and must be differentiated from bone metastasis.

The frequency of radiation pericarditis and radiation pleuritis is higher after chemoradiotherapy. Radiation myelitis is a serious and rare late complication. Radiation myelitis reportedly occurs with the spinal cord dose of only 44 Gy of concurrent chemoradiation therapy, and particular caution is thus necessary for this complication.

2. Radiotherapy for symptomatic relief

This type of radiotherapy is aimed at improving subjective symptoms and quality of life (QOL), and does not need to exert an anticancer effect. Considering the influences of radiotherapy on the patient's general condition, it is important to set the minimum necessary exposure field and total dose to reach the objective, and the treatment should be completed within as short a period of time as possible.

IX. Chemoradiotherapy

• Summary

Randomized controlled trials have demonstrated that concurrent chemoradiotherapy for esophageal carcinoma achieves a significantly higher survival rate than radiation therapy alone. Thus, this therapy is regarded as the standard for patients with esophageal carcinoma treated nonsurgically. Chemoradiotherapy with potentially curative intent is indicated for resectable T1–3, N0,1, M0 cases (UICC-TNM), unresectable T4, N0,1, M0 cases, and some M1/LYM cases. A retrospective study of concurrent chemoradiotherapy vs. surgery in resectable cases showed that this therapy was comparable to surgery. However, there have been no reports of direct comparative studies, and at present, this therapy is indicated as a therapeutic option for patients not suitable for surgery or those who prefer preservation of the esophagus. Although the drug doses, radiation doses, and treatment schedules vary among different clinical studies, the most common modality is combination chemotherapy with 5-FU and cisplatin combined with concurrent irradiation of 50–60 Gy. It is necessary to recognize that any treatment results are based on adequate chemotherapy and radiotherapy.

1. Radiation dose of definitive chemoradiotherapy

In a randomized controlled trial of radiation alone (64 Gy) and concurrent chemoradiotherapy (5-FU + cisplatin + radiation 50 Gy) carried out by the U.S. Radiation Therapy Oncology Group (RTOG), the 5-year survival rate was 0% for the former and 27% for the latter arm; the results were significantly better for chemoradiotherapy ($P < 0.0001$). Thus, it is strongly recommended to adopt chemoradiotherapy if nonsurgical treatment is to be employed. In addition, a randomized controlled trial (RTOG9405/INT0123) led by the RTOG that compared chemoradiotherapy regimens using the standard dose (50.4 Gy) and a high dose (64.8 Gy) found no superiority of the high dose to the standard dose in terms of the median survival period, 2-year survival rate, or local control rate, and concluded that the standard radiation dose for chemoradiotherapy using 5-FU + cisplatin should be 50.4 Gy (1.8 Gy 28 times). On the other hand, a number of studies performed in Japan used a dose of up to 60 Gy, and the standard radiation dose has not yet been established. For details about the radiation dose, readers should refer to the Radiotherapy section.

2. Chemotherapy used in definitive chemoradiotherapy

The standard chemotherapy regimen is 5-FU + cisplatin. In the RTOG9405 study, a course of 4-day continuous IV infusion of 5-FU at 1000 mg/m^2/day and cisplatin 75 mg/m^2 on day 1 was repeated every 4 weeks to a total of four courses (concurrent radiation was used in the initial two courses). In Japan, although the regimen of 5-FU + cisplatin is variable, a combination of 4- to 5-day continuous IV infusion of 5-FU at 700–800 mg/m^2/day plus cisplatin at 70–80 mg/m^2 is most common. In any case, two courses of concurrent chemoradiotherapy are performed, but the presence/absence of additional chemotherapy is variable. Table 8 shows the main schedules of definitive chemoradiotherapy in the major reports.

3. Adverse events caused by definitive chemoradiotherapy

Adverse events from chemoradiotherapy are broadly classified as early or late adverse events. Major early adverse events include nausea/vomiting, myelosuppression, and esophagitis. Although this therapy is safe for resectable cases, there is a risk of esophageal perforation when used for unresectable T4 cases, requiring careful management. On the other hand, late adverse events include radiation pneumonitis, pleural effusion, and pericardial effusion. Although rare, the occurrence of thoracic vertebral compression fracture or radia-

Table 8. Schedules for definitive chemoradiotherapy in major reports

Author	Target stage	Chemotherapy drugs		Radiation dose		Split
		5-FU	Cisplatin	Period × no. of courses	Single dose × no. of sessions	
RTOG	T1-4N0-1M0	1000 mg/m^2/day × 4 days	75 mg/m^2	Every 4 weeks × 4	1.8 Gy × 28	None
JCOG9708	T1N0M0	700 mg/m^2/day × 4 days	70 mg/m^2	Every 4 weeks × 2	2.0 Gy × 30	1 week
JCOG9516	T4N0-1M0	700 mg/m^2/day × 4 days	70 mg/m^2	Every 4 weeks × 2	2.0 Gy × 30	1 week
Ohtsu	T4/M1LYM	400 mg/m^2/day × 10 days	40 mg/m^2 × 2	Every 5 weeks × 2	20 Gy × 30	2 weeks
		800 mg/m^2/day × 5 days	80 mg/m^2	Every 4 weeks × 2	(Additional chemotherapy)	
Nishimura	T4M0	300 mg/m^2/day × 14 days	10 mg × 10	Every 4 weeks × 2	2.0 Gy × 30	1 week
		700 mg/m^2/day × 4 days	70 mg/m^2	Every 4 weeks × 2	(Additional chemotherapy)	

Note: Schedules without radiation split are often adopted in ongoing clinical trials in Japan

tion myelitis has also been reported (see VIII. Radiotherapy). In regard to late toxic effects, the radiation dose to at-risk organs such as the lung and heart is considered to be important. Aiming at reducing such toxic effects, the use of three-dimensional radiation planning techniques based on CT images is increasing.

4. Follow-up observation after therapy

CT and endoscopic examination are generally used for follow-up observation after definitive chemoradiotherapy. Although there is no definite evidence for the propriety of the timing of efficacy evaluation and follow-up observation, patients are usually examined 3–4 weeks after completion of chemoradiotherapy and at the end of each course of additional chemotherapy, and subsequently every 3 months during the first year and every 6 months thereafter. Residual carcinoma or recurrence is found most frequently in the local area of the esophagus, usually within a year after the beginning of therapy. As esophageal carcinoma is likely to become a so-called multiple carcinoma, it is accompanied by carcinoma in other parts of the esophagus or in the head and neck. Therefore, careful observation and appropriate responses are required.

5. Salvage therapy for local remnant or recurrent lesions after definitive chemoradiotherapy

Salvage therapy using endoscopy or surgery has recently been attempted for the treatment of local remnant or recurrent lesions after definitive chemoradiotherapy. As for salvage endoscopic treatment, the use of EMR (endoscopic mucosal resection) or PDT (photodynamic therapy) has been tried, and cured cases have been reported. However, the data available are limited, and the efficacy of this therapy has not been sufficiently demonstrated. On the other hand, salvage surgery achieves cure in some patients, but the treatment-related mortality is high, and the surgical procedure and the extent of lymph node dissection have not been established. Currently, this therapy is not used in general practice.

X. Follow-up observation after treatment of esophageal carcinoma

• Summary

The methods of follow-up observation after treatment of esophageal carcinoma depend on the initial treatment employed and the disease stage at the time of the initial treatment. It is important to formulate a strict and effective observation system, bearing in mind that early detection and early treatment of reucrrence may allow prolongation of life. It is also important to exercise caution in the development of asynchronous multiple esophageal carcinomas or asynchronous multiple carcinomas of other organs, such as is frequently seen in gastric or head and neck carcinoma.

1. Follow-up observation after EMR

Local recurrence after EMR is often seen within 1 year after the initial treatment, but it is possible after 3 or even more years. Esophageal endoscopy with Lugol staining is used for examination of local recurrence. Some reports propose examinations at 6-month intervals, whereas others recommend examinations at 3-month intervals during the first year. Lymph node recurrence and organ recurrence are often found after 3 years. Therefore, periodic as well as long-term observations are necessary. Patients should be observed at 6- to 12-month intervals using the modalities including cervical and abdominal ultrasonography (US), thoracoabdominal contrast CT, and EUS.

2. Follow-up observation after radical surgery

Recurrence after radical surgery occurs in 27%–53% of cases. Recurrence occurs within a year after surgery in 67%–79% of patients and within 2 years in 80%–98%. The mode of recurrence may be lymph nodal, local, involve an organ, or be disseminated. Combination of these also occurs frequently.

For examination of recurrence, mainly cervical and abdominal US, thoracoabdominal contrast CT and bone scintigraphy are used. Although the examination interval is 6 months in many institutions, examinations at 3- to 4-month intervals are employed according to individual patients if they are at high risk of recurrence. Generally, the follow-up period is 5 years.

3. Follow-up observation after definitive chemoradiotherapy

There have been few reports on the follow-up observation system after definitive chemoradiotherapy, and the method of follow-up is decided by each institution (see IX. Chemoradiotherapy). Besides examination of recurrence, observation for possible late adverse events related to radiotherapy is also necessary (see VIII. Radiotherapy).

4. Caution regarding asynchronous multiple esophageal carcinomas and multiple carcinomas of other organs

Esophageal carcinoma is relatively frequently accompanied by asynchronous multiple esophageal carcinomas. In addition, the occurrence of asynchronous carcinomas of other organs such as gastric or head and neck carcinoma is not rare. There is a report showing that the predominant cause of postoperative death in pN0 cases is carcinoma of other organs. Bearing this in mind, it is necessary to perform endoscopic examination of the upper gastrointestinal tract, and to observe the areas from the pharynx to the whole esophagus (remaining esophagus in resected cases) and the stomach, regularly and thoroughly. Caution regarding the development of colorectal carcinoma or other carcinomas is also necessary.

XI. Treatment of recurrent esophageal carcinoma

• Summary

In recent years, the initial treatment of esophageal carcinoma has included a wide variety of options such as endoscopic treatment, radical surgery and definitive chemoradiotherapy. Therefore, the treatment of recurrent esophageal carcinoma should be determined individually according to the type of initial treatment. In addition, treatment of recurrent carcinoma varies according to the mode of recurrence, i.e., whether it is lymph nodal, local or distant organ recurrence, and whether it is a complex type of recurrence. The general condition of the patient at the time of recurrence also influences the selection of treatment. Even when the initial treatment has been properly implemented, recurrence is not rare. Large-scale clinical trials focusing on this issue are difficult to conduct. Recurrent carcinoma may be curable depending on the type of recurrence, and aggressive treatment may be desirable. Treatment, however, often aims at suppression of tumor exacerbation or improvement of QOL.

1. Treatment of recurrence after endoscopic resection

Recent years have seen an extension of indications for endoscopic resection including EMR. Such extension may lead to a future increase in the frequency of recurrence, not only local but lymph nodal or organ recurrence.

2. Treatment of recurrence after radical surgery

Recurrence is seen in 27%–53% of patients following radical surgery. Although there are differences according to the mode of recurrence, the prognosis is generally extremely poor. The 1-year survival rate is 33%–50% for lymph node recurrence and about 25% for organ recurrence. Treatment of recurrence after radical resection is selected on the basis of the patient's general condition at the time of recurrence, the site and extent of recurrence (within or outside the scope of surgical manipulation), etc.

3. Treatment of recurrence in patients showing a complete response (CR) after definitive chemoradiotherapy

It has become more common in recent years to adopt definitive chemoradiotherapy as the initial treatment not only for unresectable but also for resectable esophageal carcinoma. Although this therapy has achieved many CR cases, local recurrence is common (see IX. Chemoradiotherapy).

XII. Palliative medicine

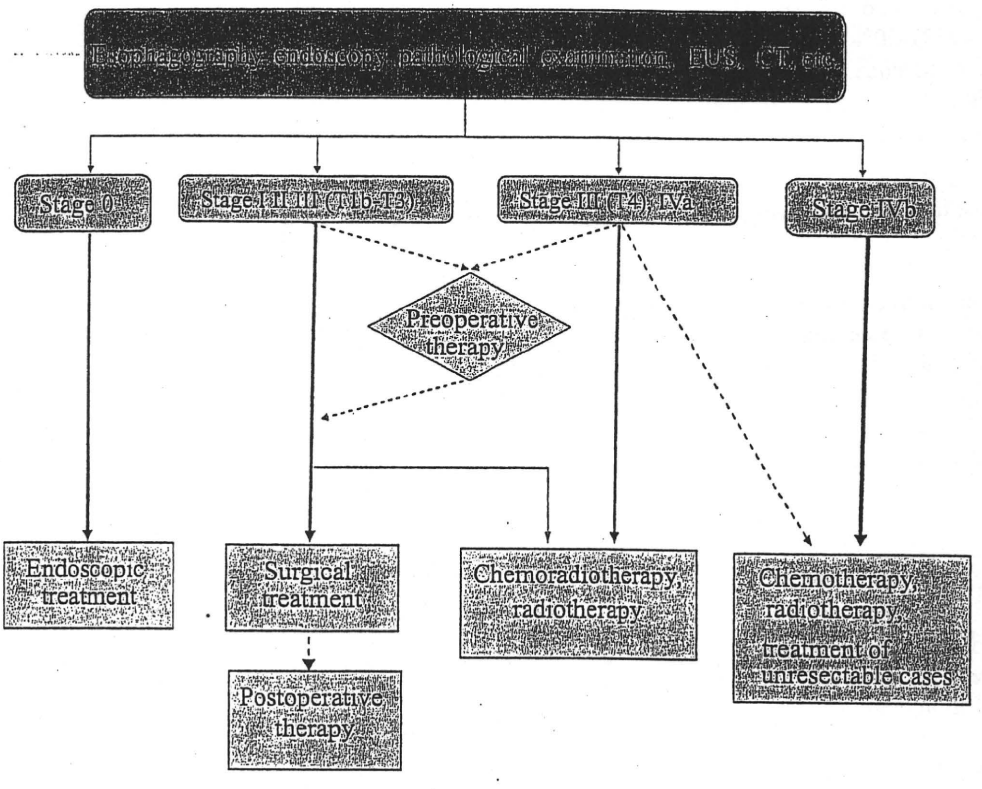
• Summary

Although palliative medicine should be provided in all fields of cancer treatment, esophageal carcinoma very frequently decreases the patient's QOL because of difficulty swallowing, malnutrition, and coughing due to a fistula, and requires considerations for procedures of symptom relief and maintenance and improvement of QOL from the initial stage of treatment. However, selection of such procedures is currently left to the discretion of each institution. Evaluation of this issue is desirable in the future.

Palliative medicine is a field designed to provide active and holistic care to patients who no longer respond to treatments aiming at cure. Palliative medicine gives top priority to control of pain and other symptoms, as well as psychological, social, and mental care of the patient, and this type of care should be provided to those in an early stage of disease as well as in the process of the main treatment (World Health Organization, WHO). This type of care is usually important for all cancer patients and is provided in daily clinical practice. Counseling by a psychooncology specialist and support from a medical social worker are also important. It is recommended that cancer pain be treated according to the Guidelines for Treatment of Cancer Pain developed by the Japanese Society for Palliative Medicine.

Important issues in palliative medicine for patients with end-stage esophageal carcinoma include symptoms described as difficulty swallowing, malnutrition and fistula formation, symptoms caused by distant metastasis, and hypercalcemia. Among these issues, relief of symptoms derived from esophageal stenosis or fistula formation may be attempted by radiotherapy, chemotherapy, (covered) stent insertion or esophageal bypass operation (see IV. Surgical treatment [D] Other treatments). There have been no studies examining the life-prolonging effects of radiotherapy or chemotherapy as compared with the best supportive care. Intravenous hyperalimentation, gastrostomy, or enterostomy may be performed to cope with malnutrition. However, there have been very few studies evaluating the efficacy and safety of these procedures in patients with esophageal carcinoma.

XIII. Algorithm for treatment of esophageal carcinoma



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Clinical Characteristics of Gastric Cancer with Metastasis to the Lymph Node along the Superior Mesenteric Vein (14v)

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Key Words

Gastric cancer · Lymph nodes along the superior mesenteric vein · Infrapyloric lymph nodes

Abstract

Aim: We investigated the clinical significance of metastasis to the lymph node (LN) along the superior mesenteric vein (14v) in gastric cancer. ***Methods:*** A retrospective study of 2,513 gastrectomy patients with a 14v dissection was done using the Ganken Igan Database. ***Results:*** The incidence of 14v metastasis correlated with tumor location, depth of tumor invasion, regional LN metastases, peritoneal metastasis, peritoneal cytology-positive, hepatic metastasis and postoperative recurrence ($p < 0.01$). Metastases to the infrapyloric LN (6), suprapyloric LN (5) and left paracardial LN (2) were independent variables affecting 14v metastasis ($p < 0.05$), and the 6 status was a useful predictive factor for a 14v-negative status with a low false-negative rate (1.9%). The patients with 14v metastasis after curative surgery demonstrated a significantly lower survival rate than those without (5-year overall survival rate; 11.3 vs. 60.2%, $p < 0.0001$). In them, LN around the abdominal aorta (16)-positive group showed a significantly lower survival rate than the negative group ($p < 0.05$). ***Conclusions:*** Advanced gastric cancer with invasion to the lower stomach often metastasizes to 14v, and the 6 status can predict 14v negative. Most patients with 14v metastasis have a poor prognosis, similar to those with systemic metastasis, although some such patients may benefit from a curative dissection.

Introduction

Radical gastrectomy with regional lymph node (LN) dissection is the only possible curative treatment for gastric cancer [1]. The status of LN metastasis is one of the most important prognostic indicators after surgery [2–5]. However, the extent of LN dissection required during gastric surgery to achieve the optimal result remains controversial [6–8]. The Dutch and the UK Medical Research Council prospective studies showed no statistical difference in survival between D1 (conventional dissection) and D2 (extended dissection), whereas a Taiwanese trial showed statistically significant improvement in survival by D2/3 in comparison to D1 [9–12]. Theoretically, the removal of a wider range of LNs by an extended dissection increases the chances for cure. Such resections, however, may not be beneficial to the prognosis if there are no LNs affected, if the cancer has developed into a systemic disease, or if a resec-

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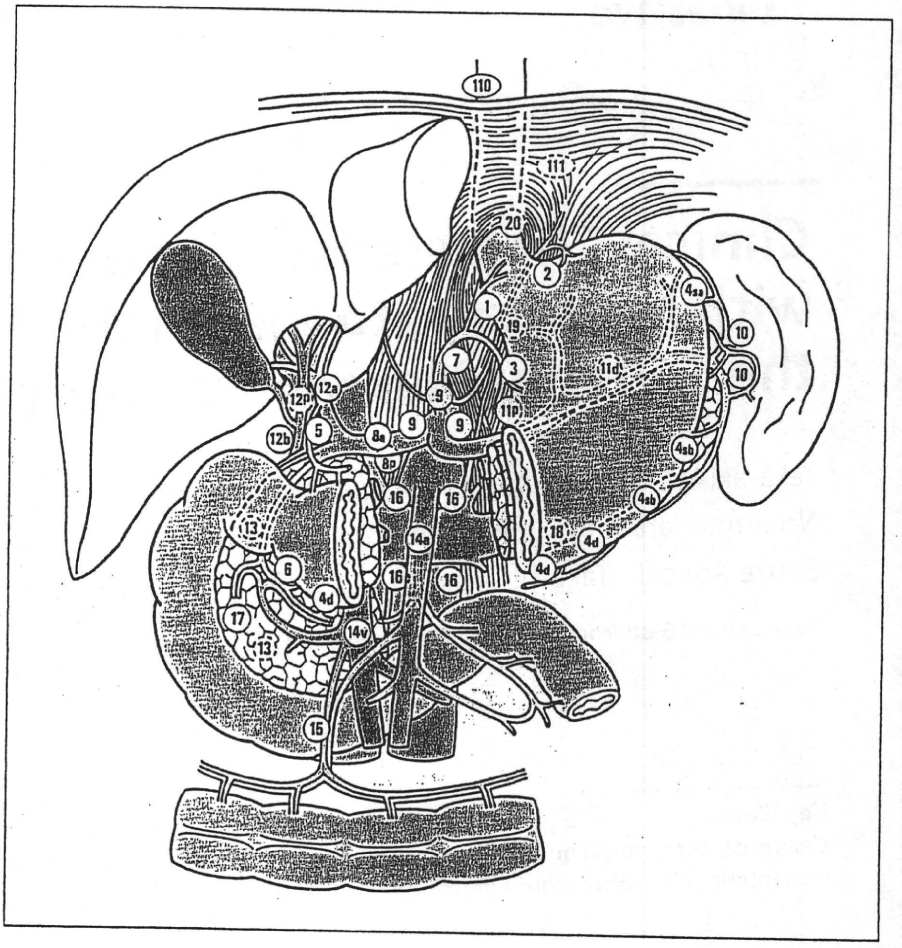

Fig. 1. Regional LN stations of the stomach [13]. 1 = Right paracardial LN; 2 = left paracardial LN; 3 = LN along the lesser curvature; 4sa = LN along the short gastric vessels; 4sb = LN along the left gastroepiploic vessels; 4d = LN along the right gastroepiploic vessels; 5 = suprapyloric LN; 6 = infrapyloric LN; 7 = LN along the left gastric artery; 8a = LN along the common hepatic artery (anterosuperior group); 8p = LN along the common hepatic artery (posterior group); 9 = LN around the celiac artery; 10 = LN at the splenic hilum; 11p = LN along the proximal splenic artery; 11d = LN along the distal splenic artery; 12a = LN in the hepatoduodenal ligament (along the hepatic artery); 12b = LN in the hepatoduodenal ligament (along the bile duct); 12p = LN in the hepatoduodenal ligament (behind the portal vein); 13 = LN on the posterior surface of the pancreatic head; 14v = LN along the superior mesenteric vein; 14a = LN along the superior mesenteric artery; 15 = LN along the middle colic vessels; 16 = LN around the abdominal aorta; 17 = LN on the anterior surface of the pancreatic head. Printed with permission from the Japanese Gastric Cancer Association.

tion would substantially increase the morbidity and mortality.

The LN along the superior mesenteric vein (14v) is one of the regional LNs of the stomach (extra-perigastric LN) [13]. In Japan, a gastrectomy with D2 has long been the standard treatment, and 14v dissection is included in surgery for advanced gastric cancer in the lower stomach [14]. However, it should be noted that a dissection of 14v has a risk of injuring the weak vessels around 14v such as the gastrocolic trunk and the middle colic vein, and consequently causing bleeding from those vessels. It would be unnecessary to dissect 14v if the dissection is not considered to clearly improve the prognosis and grading of tumor stage. However, there have so far been no studies regarding the clinical significance of 14v metastasis and the benefits of the dissection.

This study was designed to clarify the clinical features of gastric cancer with 14v metastases. In a series of patients with gastric cancer, the relationship between the metastatic status of 14v and the clinicopathological factors including the regional LNs, and the prognostic impact of 14v metastases was analyzed using the Ganken Igan Database 1946–2004, which is one of the largest databases of gastric cancer in Japan [15].

Methods

A retrospective study of 13,740 cases with gastric cancer was performed using the Ganken Igan Database 1946–2004 ('Japanese Foundation for Cancer Research's Gastric Cancer Database 1946–2004') with the permission of the editors [15]. From this group of cases, we picked 2,513 patients who had undergone a gastrectomy with a 14v dissection.

First, the frequency of pathological 14v metastasis was calculated according to the primary tumor location and the depth of tumor invasion.

Next, the relationship between 14v metastasis and the clinicopathological factors such as age, sex, tumor location, depth of invasion, histological type of tumor, peritoneal metastasis (P), peri-

Table 1. Frequency of 14v metastasis according to depth of invasion and location of gastric cancer

a Frequency of 14v metastasis according to depth of invasion

Depth of invasion	Tumor location[a]							Total
	whole	L, LD	ML, LM	M	UM, MU	U	unknown	
M, SM	0/14 (0.0)	3/171 (1.8)	2/110 (1.8)	2/176 (1.1)	0/47 (0.0)	0/16 (0.0)	0/1	7/535 (1.3)
MP, SS	6/42 (14.3)	34/248 (13.7)	51/306 (16.7)	5/104 (4.8)	4/90 (4.4)	2/43 (4.7)	0/0	102/833 (12.2)
SE	55/261 (21.1)	20/112 (17.9)	60/365 (16.4)	4/60 (6.7)	14/180 (7.8)	1/41 (2.4)	0/0	154/1,019 (15.1)
SI	15/42 (35.7)	7/14 (50.0)	12/27 (44.4)	0/0 (0)	5/23 (21.7)	0/8 (0)	0/0	39/114 (34.2)
Unknown	0/0	1/1	1/5	0/3	0/1	0/1	1/1	3/12
Total	76/359 (21.2)	65/546 (11.9)	126/813 (15.5)	11/343 (3.2)	23/341 (6.7)	3/109 (2.8)	1/2	305/2,513 (12.1)

b Frequency of 14v metastasis according to location of gastric cancer

	Tumor location/depth of invasion			
	non-low/M, SM	low/M, SM	non-low/MP or deeper	low/MP or deeper
Patients	2/292 (0.7)	5/242 (2.1)	57/758 (7.5)	238/1,208 (19.7)

Low = Region including the lower third of the stomach (whole, L, LD, ML, LM). Values in parentheses are percentages.

[a] The portion of the stomach is defined as follows by the Japanese classification [13]. U = Upper third; M = middle third; L = lower third; D = duodenum; M = mucosa; SM = submucosa; MP = muscularis propria; SS = subserosa; SE = serosa; SI = adjacent structures.

toneal cytology (CY), hepatic metastasis (H) and postoperative recurrence was investigated. Similarly, the relationship between the pathological metastatic status of 14v and that of the other regional LNs such as 1, 2, 3, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a and 16 was examined (fig. 1).

Next, the above factors were selected as potentially useful predictive factors for 14v metastasis. The predictive values of these factors for 14v metastasis were analyzed by calculating the accuracy or false-negative rate according to the method by Veronesi et al. [16].

Finally, we investigated the prognostic significance of 14v and 14v-related LNs such as 6 and 16 in the same stream of the lymphatic flow. The prognosis of the 14v-, 6- or 16-positive group was compared with the negative group in the patients who underwent curative surgery with a 5-year follow-up.

The surgical procedures and clinicopathological assessment were defined according to the 13th edition of the Japanese Classification (1998) [13]. The regional LNs of the stomach are shown in figure 1 [13]. This classification is recommended by the American Joint Committee on Cancer, in its fourth Manual for Staging of Cancer, and by the International Union against Cancer [10].

For statistical analyses, the StatView-J 5.0 software program (SAS Institute Inc., Cary, N.C., USA) was used. A logistic regression analysis was used to test univariate and multivariate associations between the variables. The survival curves were drawn according to the Kaplan-Meier method and the survival analysis was carried out using the log-rank test. All differences were defined to be significant when $p < 0.05$.

Results

Frequency of 14v Metastasis

Of the 2,513 patients who underwent a 14v dissection, 305 had 14v metastasis (12.1%). The frequency of 14v metastasis according to tumor location and the depth of invasion of primary gastric cancer are shown in table 1. In 88.5% [(65 + 126 + 76)/(305 – 1) × 100] of gastric cancer patients with 14v metastasis, the tumors had invaded the lower third of the stomach. In 97.7% [(102 + 154 + 39)/(305 – 3) × 100] of gastric cancer patients with 14v metastasis, the depth of invasion was the muscularis propria (MP) or deeper (table 1a). In advanced gastric cancer which had invaded to the MP or deeper and involved the lower third of the stomach, the frequency of 14v metastasis was 19.7% (table 1b).

Relationship between 14v Metastatic Status and Clinicopathological Factors Including the Regional LNs

14v metastasis was found to significantly correlate with the tumor location (the region including the lower third of the stomach), the depth of invasion (MP or deeper), P, CY, and H ($p < 0.05$; table 2). Moreover, a significant difference in the postoperative recurrence was found

Table 2. Relationship between metastatic status of 14v and clinicopathological factors using univariate analysis

Factors	14v metastasis		p[1]
	negative	positive	
Age (2,513)[2]			NS
<60 years	1,218 (55)	171 (56)	
≥60 years	990 (45)	134 (44)	
Sex (2,513)[2]			NS
Male	1,419 (50)	201 (66)	
Female	1,419 (50)	104 (34)	
Tumor location (2,511)[2]			<0.001
Low	1,451 (66)	267 (88)	
Non-low	756 (34)	37 (12)	
Depth of invasion (2,501)[2]			<0.001
M, SM	528 (24)	7 (02)	
MP or deeper	1,671 (76)	295 (98)	
Histological type (2,485)[2]			NS
Differentiated	917 (42)	127 (42)	
Undifferentiated	1,267 (58)	174 (58)	
P (2,513)[2]			<0.001
Absent	2,094 (95)	252 (83)	
Present	114 (05)	53 (17)	
CY (603)[2]			<0.001
Absent	433 (85)	56 (62)	
Present	79 (15)	35 (38)	
H (2,513)[2]			<0.01
Absent	2,178 (99)	294 (96)	
Present	30 (01)	11 (04)	
Postoperative recurrence (2,513)[2]			<0.001
Absent	1,712 (77)	162 (53)	
Present	496 (23)	143 (47)	

Values in parentheses are percentages. NS = Not significant; low = the region including the lower third of the stomach (whole, L, LD, ML, LM).

[1] Correlation was analyzed with a logistic regression analysis.

[2] Available number.

between the 14v-positive and the 14v-negative groups ($p < 0.05$; table 2).

The metastatic status of 14v was significantly correlated with that of all other regional LNs ($p < 0.05$; table 3). The odds ratios of 6, 16 and 8a were high (16.83, 9.01 and 8.37, respectively) in comparison to the other LNs.

The tumor location, the depth of invasion, P, CY, H and the regional LNs (1, 2, 3, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a and 16), whose univariate p values were less than 0.05, were included in a multivariate analysis to test associations with 14v metastasis. This analysis demonstrated metastases of 6, 5 or 2 to be independent variables affecting 14v metastasis ($p < 0.05$; table 4).

Predictive Value of Clinicopathological Factors for 14v Metastasis

The independent factors described above (6, 5 and 2) were selected as the candidates for useful predictive factors for 14v metastasis. The predictive value was analyzed with regard to the accuracy and false-negative rate according to the method of Veronesi et al. [16]. The accuracy of 6 was 99.0% [(1,369 + 823 + 263)/2,481 ×100]. The false-negative rate of 6 was 1.9% [26/(1,369 + 26) × 100]. Similarly, the accuracy of 5 and 2 was 91.0 and 92.5%, respectively, and the false-negative rate of 5 and 2 was 10.0 and 9.2%, respectively.

Prognostic Significance of Metastatic Status of 14v and 14v-Related LNs

In the patients who underwent curative surgery with a 5-year follow-up, the 14v-positive group demonstrated a lower rate of overall survival than the negative group ($p < 0.0001$; fig. 2a). The 5-year overall survival rate was 11.3% in the 14v-positive group and 60.2% in the negative group. Next, the prognostic significance of the metastasis to 14v-related LNs 6 and 16 in the same stream of the lymphatic flow was investigated. The 6- or 16-positive group also showed poorer prognosis than the negative group ($p < 0.0001$; fig.2b, c). The 5-year overall survival rate in the 6- or 16-positive group was 34.1 or 13.4%, respectively. In the patients with 6 metastasis, the 14v-positive group showed a lower rate of overall survival than the negative group ($p < 0.0001$; fig. 2d). In the patients with 14v metastasis, the 16-positive group showed a lower rate of overall survival than the negative group ($p < 0.05$). The 5-year overall survival rate was 8.9% in the 16-positive group and 17.5% in the negative group (fig. 2e).

Discussion

Initially, the correlation between the location of the primary tumor and the depth of invasion in gastric cancer with 14v metastasis was investigated (table 1). The 14v is subject to metastasis in gastric cancer with invasion to the lower stomach, and the frequency of 14v metastasis is higher in proportion to the depth of invasion. It is noteworthy that the frequency of 14v metastasis reaches about 20% in advanced gastric cancer with invasion to the lower stomach. In such an advanced gastric cancer, 14v would have to be dissected in order to perform a curative resection if the dissection is to have either a prognostic or clinical benefit.