Table 4 Efficacies of major combination therapies

Drug	Histologic type	No. of cases	Response rate (%)
5-FU + cisplatin	Squamous cell carcinoma	39	36
Cisplatin + paclitaxel[a]	Squamous cell carcinoma/adenocarcinoma	32	44
Cisplatin + irinotecan[b]	Squamous cell carcinoma/adenocarcinoma	35	57
Cisplatin + gemcitabine[b]	Squamous cell carcinoma/adenocarcinoma	32	45
5-FU + nedaplatin	Squamous cell carcinoma	38	40

[a] This regimen is approved through public knowledge-based application (as of February 2012)

[b] This regimen is not approved for insurance coverage (as of February 2012)

combination regimen is 5-FU + cisplatin. In other countries, this combination therapy is usually administered as follows: continuous intravenous infusion of 5-FU at 1,000 mg/m^2/day for 4–5 days, plus intravenous cisplatin at 100 mg/m^2 on day 1. In contrast, a phase II clinical trial of 5-day continuous intravenous infusion of 5-FU at 700 mg/m^2/day plus intravenous cisplatin at 70 mg/m^2 on day 1 carried out in Japan showed a response rate of 36 %. A comparison between this combination therapy and best supportive care carried out overseas demonstrated no definite prolongation of survival in the former group. However, this study included many patients in whom this therapy was used mainly as adjuvant chemotherapy. However, it excluded those in whom the metastatic focus in the liver accounted for more than 30 % of the hepatic parenchyma and those who had peritoneal dissemination. Therefore, the effect of this combination therapy on survival remains unclear. Although in recent years, regimens containing paclitaxel, irinotecan, or gemcitabine have been tried overseas, and regimens using nedaplatin or docetaxel have been tried in Japan, no large-scale phase III trials of these regimens have been carried out. Thus, the merits of these regimens over 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 the first-line treatment, followed by docetaxel as a second-line treatment. In any event, the effect of the use of chemotherapy alone, regardless of whether it is combination therapy or monotherapy, is limited, and chemotherapy not combined with other treatment modalities is applied only to patients with unresectable metastatic lesions.

Cisplatin, a chemotherapeutic drug that is in wide use, is classified as a highly pro-emetic drug. Guidelines for appropriate use of antiemetic drugs recommend the triple-drug combination of a 5-HT$_3$ receptor antagonist, corticosteroid, and aprepitant to prevent emesis while using cisplatin. For other drugs, it is necessary to check the risk of emesis against guidelines for appropriate use of antiemetic drugs and to take appropriate prophylactic measures.

Radiotherapy

Summary

As compared to radiation monotherapy, concurrent chemoradiotherapy significantly increases the survival rate, although radiotherapy administered sequentially after induction chemotherapy does not. Concurrent chemoradiotherapy is indicated for patients with T1-4N0-3M0 carcinoma (UICC-TNM classification, 2009 edition) in good general condition and for those with locally advanced carcinoma up to metastasis to the supraclavicular lymph nodes (M1). However, the risk of serious complications such as fistula formation is high in cases of unresectable locally advanced carcinoma (T4).

Because prolongation of the duration of irradiation decreases the local control rate of radiation monotherapy, it is important to complete irradiation using a definitive dose (66–68.4 Gy) within 7 weeks. In definitive concurrent chemoradiotherapy, the use of at least 50 Gy/25 fractions/5 weeks with a conventional fractionation protocol is necessary. The standard radiation dose for concurrent chemoradiotherapy in the USA is 50.4 Gy/28 fractions. In contrast, in Japan, the standard radiation dose is 60 Gy/30 fractions/6–8 weeks for concurrent chemoradiotherapy, and its safety has already been demonstrated.

A randomized controlled trial carried out in Japan revealed that concomitant use of external beam radiation and intracavitary radiation is effective for patients with T1–2 esophageal carcinoma, a relatively early stage of the disease. However, recently chemoradiotherapy is used commonly, and the available evidence is not sufficient to recommend the addition of intracavitary radiation to chemoradiotherapy.

Previously, radiotherapy was primarily used for patients who were not suitable candidates for surgery or endoscopic mucosal resection (EMR). However, in recent years, radiotherapy (in particular, chemoradiotherapy) has been widely used for both superficial carcinoma and locally advanced carcinoma, as definitive treatment.

The standard radiotherapy used for esophageal carcinoma is in accordance with the Radiotherapy Planning Guidelines 2008 (ed. by Japanese College of Radiology, The Japanese Society for Therapeutic Radiology and Oncology, and Japan Radiological Society). The key points are described below.

Definitive radiotherapy

Indications

A definitive radiotherapy protocol is used when control of all gross lesions leading to cure is expected. Definitive irradiation is the most suitable for cases with T1-4N0-3M0 carcinoma (UICC-TNM classification, 2009 edition) and cases with locally advanced disease up to metastasis to the supraclavicular nodes (M1). In patients with a favorable general condition allowing combined use of chemotherapy, the standard treatment is chemoradiotherapy rather than radiation monotherapy.

Definitive chemoradiotherapy has been used for the treatment of postoperative recurrence in the regional lymph nodes in patients without distant metastasis or postoperative residual tumor, as well as for definitive irradiation in fresh cases. It has been shown to provide favorable therapeutic results.

Target volume

Gross tumor volume (GTV) GTV includes the esophageal primary foci (GTV primary) and metastatic lymph nodes (GTV nodal) as determined by endoscopy and CT. In cases of esophageal carcinoma, it is difficult to determine the presence of lymph node metastasis on the basis of the sizes of the lymph nodes. However, it has been reported to be relatively safe to treat lymph nodes measuring 5 mm or more in the minor axis as determined by CT or MRI, regarding them as metastatic foci, to decrease the percentage of false-negative cases.

^{18}F-fluorodeoxyglucose (FDG)-PET is useful for staging because it allows the detection of hidden distant metastases. However, the sensitivity and specificity of this technique to detect metastatic lymph nodes are not always high in cases of esophageal carcinoma; therefore, it may not be reasonable to attempt to identify metastatic lymph nodes on the basis of PET findings alone for treatment planning. On the positive side, it has been reported that PET/CT can confirm the extent of the primary focus (GTV primary) better than those based on CT alone, if the threshold of FDG activity is set properly.

Clinical target volume 1 (CTV1) CTV1 is defined as the entire circumference of the esophagus including the GTV primary on endoscopy or CT, as well as possible microscopic lesions within 3–4 cm cephalocaudally and regional lymph nodes. A study of resected specimens of esophageal squamous cell carcinoma in 34 patients showed that the mean extent of microscopic invasion from the GTV primary was 10.5 ± 13.5 mm. It has been reported that a CTV margin of 3 cm would cover the aforementioned extent of microscopic progression in 94 % of patients.

However, because EP and LPM lesions in cases of T1a carcinoma rarely metastasize to the lymph nodes, irradiation of regional lymph nodes is not required. By contrast, lymph node metastasis is present in 10–50 % of cases of MM or SM superficial carcinomas. Therefore, prophylactic irradiation of the regional lymph nodes is required for these cases, as for cases of advanced esophageal carcinoma. Table 5 lists the standard CTV1 in relation to the site of the primary lesion. Currently, there is not enough evidence and there is no evidence-based consensus on which lymph node regions the CTV should extend to. The irradiation dose to these areas should be 40–46 Gy/20–23 fractions. In regard to chemoradiotherapy for superficial esophageal carcinoma (cT1N0M0), it has been reported that favorable therapeutic results can be obtained by localized irradiation, allowing a 3-cm margin inferiorly and superiorly, and a 1- to 2-cm margin anteriorly, posteriorly, and on both sides of the primary focus (GTV primary). Thus, extensive irradiation of regional lymph nodes may not be necessary for superficial esophageal carcinoma.

Clinical target volume 2 (CTV2) CTV2 after irradiation of 40–46 Gy to CTV1 should cover the whole circumference of the esophagus including the GTV primary with addition of a margin of about 2 cm in the cephalocaudal direction and 0–0.5 cm in the lateral direction, and the area of metastatic lymph nodes (GTV nodal) with an additional margin of about 0–0.5 cm in the lateral direction.

Planning target volume 1 (PTV1) The planning target volume at the beginning of radiotherapy (PTV1) should include CTV1 with an adequate margin (0.5–1.0 cm in the lateral direction and 1–2 cm in the cephalocaudal direction), allowing for respiratory movements and errors in reproducing the patient's fixation. Because respiratory movements are particularly large in the case of lower thoracic esophageal carcinoma, a margin of 0.8 cm in the lateral direction and 1.8 cm in the cephalocaudal direction has been reported to be necessary.

Planning target volume 2 (PTV2) The planning target volume for the reduced exposure field at 40–46 Gy (PTV2) should include CTV2 with an adequate margin (0.5–1.0 cm in the lateral direction and 1–2 cm in the cephalocaudal direction).

Table 5 Standard lymph node regions in relation to the site of the primary focus (CTV1)

Cervical esophagus (Ce)	From the midsdle deep cervical lymph nodes [102-mid] to the lymph nodes at the tracheal bifurcation [107]
Upper thoracic esophagus (Ut)	From the supraclavicular lymph nodes [104] to the middle thoracic paraesophageal lymph nodes [108]
Middle thoracic esophagus (Mt)	a. From the supraclavicular lymph nodes [104] to the lower thoracic paraesophageal [110] or perigastric lymph nodes b. From the lymph nodes along the recurrent laryngeal nerve [106-rec] and upper thoracic paraesophageal lymph nodes [105] to the lower thoracic paraesophageal [110] or perigastric lymph nodes
Lower thoracic esophagus (Lt)	From the lymph nodes along the recurrent laryngeal nerve [106-rec] and upper thoracic paraesophageal lymph nodes [105] to the perigastric lymph nodes
Patients of advanced age or with complications	Only lymph node regions around the primary focus

Locations of regional lymph nodes of the esophagus on CT images are shown in the 10th edition of the Japanese Classification of Esophageal Cancer

Perigastric lymph nodes: Cardiac lymph nodes [1,2], lymph nodes along the lesser curvature [3], and lymph nodes along the left gastric artery [7]

There is no consistent consensus on CTV1 in cases of primary carcinoma originating in the middle thoracic esophagus (Mt)

Radiotherapy planning and the irradiation method

Three-dimensional treatment planning based on CT images is recommended. This method allows an understanding of the 3-dimensional positional relationship between the target volume and the organs at risk, and is useful for implementing high-accuracy radiotherapy to minimize exposure of the organs at risk. If a lesion cannot be visualized by CT, as in the case of superficial carcinoma, clipping to the upper and lower parts of the lesion under endoscopic guidance is required prior to CT imaging. Organs at risk that require particular attention in treatment planning for esophageal carcinoma include the lung, heart, and spinal cord.

The use of 6–10 MV X-rays is recommended for external irradiation. An appropriate point in the PTV is chosen as the dose assessment point. Irradiation should be applied while restricting the cumulative maximum dose to the spinal cord to 44–46 Gy or less by using the fixed multiple field technique or by changing the radiation field midcourse. Intensity-modulated radiotherapy (IMRT) may be used for the treatment of cervical esophageal carcinoma at facilities that have radiation oncologists and medical physicists who are familiar with treatment planning to secure adequate quality control of radiotherapy.

Dose fractionation

In general, the conventional fractionation method is used. The standard radiation dose for chemoradiotherapy used overseas is about 50 Gy/25–28 fractions/5–6 weeks. In contrast, in Japan, the standard radiation dose is about 60 Gy/30 fractions/6–8 weeks for chemoradiotherapy, and 60–70 Gy/30–35 fractions/6–7 weeks for radiation monotherapy. Chemoradiotherapy is described in detail in chapter XI.

The overall treatment time is an important factor in radiotherapy for esophageal squamous cell carcinoma. The local control rate is known to decrease with increase in the overall treatment time of radiotherapy; therefore, in cases of radiation monotherapy, it is important to avoid prolongation of the overall treatment time as much as possible.

Intracavitary radiation

In Japan, superficial esophageal carcinoma is considered to be a suitable indication for intracavitary irradiation, because this technique of irradiation can deliver sufficient radiation dose to the superficial lesions. A retrospective analysis from a single institution indicated that a radiation boost by intracavitary irradiation for a superficial lesion of the esophagus yielded favorable therapeutic results. However, the report by Nemoto et al., who reviewed multicenter studies carried out in Japan, indicated that there was no difference in the survival rate between external radiation monotherapy and external radiotherapy combined with intracavitary irradiation in patients with superficial carcinoma of the esophagus. While randomized controlled trials focusing on superficial esophageal carcinoma have never been done, randomized controlled trials of intracavitary irradiation for esophageal carcinoma, including advanced cases in Japan, reported that intracavitary irradiation was effective for esophageal carcinomas measuring 5 cm or less in the major axis or those with a depth of invasion corresponding to T1 or T2. However, more recently, chemoradiotherapy has come to be used commonly, and the efficacy and safety of an additional intracavitary radiation boost to chemoradiotherapy are not necessarily clear.

For intracavitary irradiation, a balloon applicator measuring 15–20 mm in diameter should be used to avoid uneven distribution of the radiation source. The point of dose assessment should be 5 mm lateral to the applicator surface (5 mm submucosal), and the dose on the mucosal surface should also be reported. Although there is no definite consensus about the optimal dose and fractionation of intracavitary irradiation because they are closely related to the combined external irradiation dose, the general practice is external irradiation at 50–60 Gy followed by intracavitary irradiation at 8–12 Gy/2–4 fractions (3–4 Gy per session). Because an increase in the fractional dose of intracavitary radiation is associated with an increased risk of late complications, such as esophageal ulcers and perforation, 1–2 sessions per week at a dose of 4 Gy or less per session for high-dose-rate irradiation, or at a dose of 6 Gy or less per session for low-dose-rate irradiation is recommended.

Complications

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

As late adverse events, esophageal perforation and bleeding occur in some patients treated by radiotherapy. The incidence rate of late adverse events is relatively increased in cases of T4 disease. In cases where high-dose intracavitary irradiation is employed, special caution concerning the occurrence of esophageal ulcers and perforation is necessary. The incidence of these conditions has been reported to be increased in patients given intracavitary irradiation after chemoradiotherapy. Esophageal stenosis may occur in patients with circumferential disease or those subjected to repeated EMR. Because radiation pneumonia may be fatal in patients of advanced age, it is necessary to reduce the exposure dose to the lung in treatment planning. The possibility of thoracic vertebral compression fracture within the radiation field requires particular attention and should be differentiated from bone metastasis.

Pericardial effusion and constrictive pericarditis associated with radiation epicarditis and pleural effusion caused by radiation pleuritis have been reported to occur at high frequencies after chemoradiotherapy. Radiation myelitis is a serious and rare late complication. There are case reports of radiation myelitis developing even in cases with an exposure dose to the spinal cord of only 44 Gy, suggesting the need for particular vigilance regarding this complication. In addition, irradiation of the cervical area may cause hypothyroidism a few years post-irradiation. Because hypothyroidism may serve as a risk factor for radiation epicarditis and radiation pleuritis, regular monitoring of the thyroid functions is necessary in long-surviving patients.

Radiotherapy for symptomatic relief

This type of radiotherapy is aimed at improving the subjective symptoms and QOL and not at obtaining an anticancer effect. Radiotherapy may be used for the primary focus to improve dysphagia in patients with esophageal carcinoma, or for the treatment of distant metastases such as bone metastasis and brain metastasis. Although intracavitary irradiation monotherapy has been suggested to be useful for improving dysphagia, this radiotherapeutic technique is seldom used for the management of dysphagia associated with esophageal carcinoma in Japan.

For palliative irradiation, it is important to set the minimum necessary radiation field and total dose to achieve the treatment objective. The treatment should be completed within as short a period of time as possible, considering the general condition of the patient.

Chemoradiotherapy

Summary

Randomized controlled studies have demonstrated that chemoradiotherapy yields a significantly higher survival rate than radiation monotherapy in patients with esophageal carcinoma; therefore, this therapeutic modality is regarded as the standard therapy for patients with esophageal carcinoma when non-surgical treatment is the choice. Patients who can be the target of definitive chemoradiotherapy include T1-3N0-3M0 cases (UICC-TNM classification, 2009 edition), unresectable T4N0-3M0 cases, and cases with locally advanced disease up to metastasis to the supraclavicular nodes (M1). Some reports showed no significant difference in the overall survival and recurrence-free survival between patients with resectable lesions treated by chemoradiotherapy or by surgery alone. However, in Japan, neoadjuvant chemotherapy followed by surgery is considered to be superior to chemoradiotherapy in patients with Stage IB–III disease (UICC-TMN classification, 2009 edition), while the equivalence of chemoradiotherapy and surgery is considered in patients with Stage IA disease (T1N0M0, UICC-TNM classification, 2009 edition). Although the drug doses, radiation doses, and treatment schedules vary among different clinical studies, the most common protocol employed is combined chemotherapy with 5-FU plus cisplatin and concurrent radiotherapy at a total dose of 50-60 Gy. It is necessary to recognize that any of the reported treatment results can be reproducible only

when the chemotherapy and radiotherapy defined in the study are adequately applied.

Radiation dose in definitive chemoradiotherapy

In a randomized controlled trial of radiation monotherapy (64 Gy) and concurrent chemoradiotherapy (5-FU + cisplatin + radiation 50 Gy) for T1-4N0-1M0 esophageal carcinoma (corresponding to UICC-TNM classification, 2002 edition) carried out by the US Radiation Therapy Oncology Group (RTOG), the 5-year survival rate was 0 % for the former and 26 % for the latter; the latter treatment yielded significantly better results ($p < 0.0001$). Thus, chemoradiotherapy is strongly recommended in non-surgical treatment. In regard of the timing of chemotherapy and radiotherapy, a meta-analysis showed that concurrent chemoradiotherapy is associated with a significantly lower mortality rate ($p < 0.0001$) than sequential chemoradiotherapy. In addition, a randomized controlled study (RTOG9405/INT0123) carried out succeedingly to RTOG 85-01 that compared chemoradiotherapy using standard-dose (50.4 Gy) and high-dose (64.8 Gy) radiation in patients with T1-4N0-1M0 esophageal carcinoma (corresponding to UICC-TNM classification, 2002 edition) revealed no superiority of high-dose radiation over standard-dose radiation in terms of the median survival time, the 2-year survival rate, and the local control rate, and concluded that the standard radiation dose for chemoradiotherapy using a combination of 5-FU plus cisplatin should be 50.4 Gy (1.8 Gy × 28 times). By contrast, a radiation dose of 60 Gy has been used predominantly in studies carried out in Japan. Although the standard radiation dose has not yet been established in Japan, change to 1.8 Gy/fraction × 28 times (total dose of 50.4 Gy) is now under review at some facilities. For information on the method of irradiation and dose fractionation, see "Radiotherapy".

Chemotherapy used in definitive chemoradiotherapy

The standard chemotherapy regimen is 5-FU + cisplatin. In the aforementioned RTOG9405/INT0123 study, a course of 4 days' continuous intravenous infusion of 5-FU at 1,000 mg/m^2/day plus intravenous cisplatin at 75 mg/m^2 on day 1 was repeated every 4 weeks up to a total of 4 courses (concurrent radiation was used in the initial 2 courses). In Japan, although use of the 5-FU + cisplatin regimen is variable, a phase II clinical study (JCOG9708) of chemoradiotherapy (5-FU + cisplatin + irradiation of 60 Gy) for cases of Stage I esophageal carcinoma (T1N0M0, UICC-TNM classification, 1997 edition [*corresponding to Stage IA: T1N0M0 in the 2009 edition]) conducted by the JCOG used 2 courses of 4 days' continuous intravenous drip infusion of 5-FU at 700 mg/m^2/day plus intravenous drip infusion of cisplatin at 70 mg/m^2 on day 1 repeated every 4 weeks. In the JCOG9708 study, the complete response rate was 87.5 %, the 4-year survival rate was 80.5 %, and the 4-year progression-free survival rate was 68 %, suggesting results equivalent to those of surgery. Currently, a phase III clinical study (JCG0502) comparing chemoradiotherapy with surgery is underway. In another phase II JCOG study (JCOG9906) of chemoradiotherapy (5-FU + cisplatin + irradiation of 60 Gy) performed in cases of resectable Stage II–III esophageal carcinoma, a course of 5 days' continuous intravenous infusion of 5-FU at 400 mg/m^2/day for 2 weeks plus intravenous cisplatin at 40 mg/m^2 on days 1 and 8 was repeated every 5 weeks for a total of 4 courses (the initial 2 courses were combined with concurrent irradiation). However, the use of chemotherapy according to the RTOG regimen is now under consideration in Japan. In any case, 2 courses of concurrent chemoradiotherapy are commonly administered. Although the use of additional chemotherapy after chemoradiotherapy is variable; 2 courses of additional chemotherapy are often administered for Stage II–III lesions. Table 6 shows the main schedules used in definitive chemoradiotherapy.

Adverse events associated with definitive chemoradiotherapy

Adverse events associated with chemoradiotherapy may be attributable to chemotherapy, radiotherapy, or both, and it is difficult to strictly distinguish among these causes. Major early adverse events include nausea, vomiting, myelosuppression, esophagitis, stomatitis, diarrhea, constipation, and radiation pneumonitis. In particular, radiation pneumonitis may be fatal, and it is desirable to identify factors that may predict the development of this condition. In this regard, it has been suggested that dose–volume histogram (DVH) parameters of irradiation may be useful. On the other hand, late adverse events include radiation pericarditis, radiation pleuritis, pleural effusion, and pericardial effusion. Hypothyroidism may occur in patients who have received radiation in the cervical area, which may also be accompanied by pleural effusion or pericardial effusion, necessitating caution. Although rare, the occurrence of thoracic vertebral compression fracture or radiation myelitis has also been reported (see "Radiotherapy"). In regard of the late toxic effects, it is considered that the radiation dose to organs at risk such as the lung and heart should be carefully considered. Use of a 3-dimensional radiation planning technique based on CT images aimed at reducing the toxic effects is now common.

Among other possible adverse events during chemoradiotherapy for esophageal carcinoma, special attention should be paid to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) attributable to cisplatin and leukoencephalopathy attributable to 5-FU. Early

Table 6 Main schedules used in definitive chemoradiotherapy

Author	Target stage	Chemotherapy drugs		Radiation dose		
		5-FU	Cisplatin	Period × No. of courses	Single dose × No. of sessions	Split
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
JCOG9906	T1N1M0 or T2-3N0-1M0	400 mg/m^2/day × 10 days	40 mg/m^2 × 2	every 4 weeks × 2	2.0 Gy × 30	2 week
Ohtsu	T4/M1/LYM	400 mg/m^2/day × 10 days	40 mg/m^2 × 2	every 5 weeks × 2	2.0 Gy × 30	2 weeks
Nishimura	T4M0	300 mg/m^2/day × 14 days	10 mg/m^2	every 4 week × 2	2.0 Gy × 30	1 week
JCOG0303	T4/M1LYM	700 mg/m^2/day × 4 days	70 mg/m^2	every 4 weeks × 2	2.0 Gy × 30	1 week
KROSG0101	Stage II–IVA	700 mg/m^2/day × 5 days	70 mg/m^2	every 4 weeks × 2	2.0 Gy × 30	1 week
Nakajima	Stage II/III	1,000 mg/m^2/day × 4 days	75 mg/m^2	every 4 weeks × 4	1.8 Gy × 28	None

Schedules without radiation split are being adopted in several ongoing clinical trials in Japan

detection and prompt medication, particularly prompt discontinuation of medication if the patient is on some drug therapy, are necessary.

Follow-up after therapy

Contrast-enhanced CT and endoscopic examination are generally used for follow-up observation after definitive chemoradiotherapy. Although there is no definitive evidence for the appropriate timing of the response evaluation and follow-up observation, patients are usually examined 3–4 weeks after completion of chemoradiotherapy at the end of each course of additional chemotherapy, and subsequently every 3 months during the first year, and every 4–6 months thereafter. Residual carcinoma or recurrence after chemoradiotherapy is found most frequently in the primary tumor in the esophagus and in the lymph nodes, usually within 1–2 years after the start of therapy. Therefore, if salvage therapy is considered, evaluation of the primary site is important. The initial endoscopic evaluation of the primary site within 75–90 days after the start of chemoradiotherapy, followed by a second evaluation within 1 month of the initial evaluation, is considered to be most effective in determining the presence/absence of exacerbation and judging whether a CR has been achieved. Because patients with esophageal carcinoma are known to show a relatively high likelihood of developing multiple carcinomas, with carcinomas developing de novo in other parts of the esophagus or in other organs (head and neck region, stomach, large intestine), careful follow-up observation and appropriate diagnostic measures are required.

Salvage therapy for local remnant or recurrent lesions after definitive chemoradiotherapy

Salvage therapy using endoscopy or surgery has recently been tried for the treatment of local remnant or recurrent lesions after definitive chemoradiotherapy (see "Salvage surgery"). As for salvage endoscopic treatment, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and photodynamic therapy (PDT) have been tried, and favorable long-term results with acceptable safety have been reported. However, the indications for these treatments and selection of the appropriate treatment method have not yet been adequately evaluated. Salvage surgery (see "Salvage surgery") provides cure in some cases; however, the incidence of operation-related adverse events and operation-related mortality is high, and the optimal surgical technique and extent of lymph node dissection have not yet been established. Therefore, salvage surgery is not employed in general practice. It has been reported that long-term survival may be achieved after salvage surgery when the depth of invasion of the residual or recurrent lesion is shallow, or when there is no residual or recurrent lymph node metastasis. To facilitate early detection of remnant or recurrence of the primary focus after definitive chemoradiotherapy, strict follow-up by endoscopy is necessary, bearing in mind the observations that the greater the T factor of the pretreatment staging, the more likely recurrence is, and that recurrence often occurs in the form of submucosal tumor-like elevation.

Diagnosis and treatment of Barrett's esophagus and Barrett's carcinoma

Summary

Esophagus showing Barrett's mucosa is called Barrett's esophagus. Barrett's mucosa refers to the columnar epithelial metaplasia that extends from the stomach to the esophagus in a continuous fashion and can be confirmed by endoscopy. Histological confirmation of specific columnar epithelial metaplasia is not required. Histologically,

Barrett's mucosa exhibits one of the following features: (1) proper esophageal glands or ducts beneath the overlying columnar epithelium; (2) squamous epithelial islets in the columnar epithelium; (3) double structure of the lamina muscularis mucosae. Barrett's carcinoma is defined as adenocarcinoma occurring in Barrett's mucosa. The definitions of early, superficial, and advanced carcinomas are the same as those of esophageal carcinoma, regarding the deep-seated lamina muscularis mucosae as the original lamina muscularis mucosae. Treatment of Barrett's carcinoma is planned in accordance with the treatment of squamous cell carcinoma of the esophagus at the same location in the esophagus. Endoscopic resection is indicated for lesions confined to the lamina propria mucosae (EP, SMM, and LPM). Relative indications are currently under consideration.

Diagnosis and treatment of double carcinoma (head and neck, stomach)

Summary

Patients with esophageal carcinoma frequently develop carcinoma of other organs, particularly of the upper aerodigestive tract, including head and neck carcinoma, gastric carcinoma, and lung carcinoma. Preoperative examination and postoperative follow-up must be carried out bearing in mind the possible presence of double/multiple lesions. Therapeutic strategies and problems involved in treatment vary widely according to the type, stage, and time of onset of the other lesions. It is important to select the surgical technique and the treatment method in a well-balanced manner, taking into consideration the general condition of the patient, and the prognosis of the esophageal lesions and second primary lesions.

Double carcinoma is defined as the co-existence of two primary carcinomas in different organs. Patients with esophageal lesion are reported to show a higher incidence of double carcinoma as compared to the incidence of malignancy in the general population. This higher incidence of double carcinoma in esophageal carcinoma patients may be explained by the sharing of risk factors of carcinomas of the upper aerodigestive tract. We would also like to emphasize the concept of field cancerization here.

The incidences and types of double carcinoma vary according to the year of survey, the duration of observation, and the specialization level of the facilities. According to the national registry of the Japan Esophageal Society, about 20 % of patients with esophageal lesion have a second primary lesion, being synchronous in 8 % and metachronous in 12.2 % of the cases. The most frequent type of double carcinoma was gastric lesions, followed by head and neck lesions (pharyngeal carcinoma), colorectal lesions and lung lesions, in descending order of frequency.

In addition, according to the 2007 statistics of the Japanese Association for Thoracic Surgery, the incidence of double carcinoma, including second primary carcinomas preceding esophageal carcinoma but excluding the ones following esophageal carcinoma, was 12.9 %, with the proportion of synchronous double lesions at 7.45 %. The type of double lesions was most frequently gastric lesions, followed by head and neck lesions.

From the viewpoint of diagnosis and treatment of esophageal lesions, the presence/absence of a second primary head and neck lesions is an important issue. A number of studies on double carcinoma in the esophagus and the head and neck region have so far been reported. Some reports claim that head and neck carcinomas may be the most frequently occurring second carcinoma in association with esophageal carcinoma.

Among patients with esophageal lesions, most studies report a frequency of head and neck lesions of about 10 %, with pharyngeal lesions the most frequent type of head and neck lesions encountered in these cases. Some characteristic features that may help in predicting the presence of head and neck lesions in patients with esophageal lesions include the presence of multiple esophageal lesions and the existence of multiple zones in the esophagus showing negative iodine staining.

In recent years, advances in endoscopic techniques, including magnifying endoscopy and image-enhanced endoscopy and increased attention to the head and neck region in patients with esophageal carcinoma, have increased the detection rate of head and neck carcinoma in the early stage by endoscopic examination of the upper gastrointestinal tract. Image-enhanced endoscopy has recently been introduced in the field of otorhinolaryngology, and the usefulness of this technique as compared to conventional white-light endoscopy has been reported.

Although esophageal carcinoma and gastric carcinoma share few risk factors, smoking is said to be a common risk factor for both esophageal carcinoma and gastric carcinoma. The high prevalence of atrophy of the gastric mucosa due to *Helicobacter pylori* infection and the high morbidity rate of gastric carcinoma due to environmental factors in Japan may exert a great influence to incidence of concomitant gastric lesion with esophageal cancer.

As a part of double/multiple carcinomas, carcinomas developing in the gastric tube after esophageal reconstruction pose another important problem.

When carrying out pretreatment examination of patients with esophageal carcinoma, due caution is necessary, because double carcinomas frequently involve areas that may greatly influence the choice of the particular therapeutic strategies used.

Follow-up observation after treatment of esophageal carcinoma

The purposes of follow-up observation after treatment of esophageal carcinoma are (1) early detection and early treatment of recurrence and (2) early detection and early treatment of multiple esophageal carcinomas and double carcinomas involving other organs. In addition, follow-up observation is important from the point of view of general management of the patient after treatment and maintaining the patient's QOL.

The methods used for follow-up observation after treatment of esophageal carcinoma depend on the initial treatment employed and the stage of the disease at the time of the initial treatment. The patient follow-up is important for possible recurrence, bearing in mind the fact that early detection and early treatment of recurrence may allow prolongation of life. It is also important to exercise caution for the development of metachronous multiple esophageal carcinoma or metachronous multiple carcinoma of other organs, such as gastric carcinoma or head and neck carcinoma. Formulation of an effective follow-up protocol based on general agreements by many doctors in Japan and verification of its efficacy are required.

Follow-up observation after endoscopic resection

Because the indications and types of additional treatment after endoscopic resection vary, and a substantial number of patients undergo follow-up observation alone, there is no standard method for follow-up observation. Local recurrence after endoscopic resection is often seen within 1 year after the initial treatment, but may also occur after 2–3 years. Therefore, long-term follow-up is necessary. Esophageal endoscopy with iodine staining is mainly used for the detection of local recurrence. Although some reports propose examinations at 6-month intervals, other reports recommend examinations at 3-month intervals during the first year after resection. Patients who undergo fractional resection or who have multiple zones of negative iodine staining require more detailed endoscopic examination of the esophagus. Lymph node recurrence and organ recurrence may be found after 2–3 years; therefore, periodic long-term observation is necessary.

Patients should be followed up at 6- to 12-month intervals by cervical and abdominal ultrasonography, thoracoabdominal contrast CT, and/or EUS. Follow-up methods after endoscopic resection suggested by JCOG0508 study (phase II study on efficacy of combined treatment of endoscopic mucosal resection [EMR] and chemoradiotherapy for clinical Stage I esophageal carcinoma [T1N0M0]) included clinical examination, cervical to abdominal contrast-enhanced CT, and measurement of the serum levels of the tumor marker SCC every 4 months until 3 years after EMR.

Follow-up observation after radical surgery

Recurrence after radical surgery has been reported to occur in 28–47 % of patients in Japan. A recurrence rate of 50 % or more is not rare in reports from Europe and North America. Among patients with recurrence, the timing of recurrence is within 1 year after surgery in 54–79 % of patients and within 2 years after surgery in 80–98 % of patients. Although rare, recurrence after more than 2 years can also occur, necessitating caution. The mode of recurrence may be lymph node metastasis, local recurrence, organ metastasis, or disseminated recurrence; a combination of these is also encountered frequently.

Currently, the actual follow-up protocol employed after radical surgery for esophageal carcinoma is left to the discretion of the treating facility. There are no reports of the benefit of regular follow-up observations or of effective methods of follow-up observation. Examination for recurrence basically consists of head and neck US, thoracoabdominal contrast-enhanced CT, and bone scintigraphy. At many facilities, examination by US or CT is repeated every 3–6 months, often with some variations of the intervals according to the degree of progression and the number of years elapsed after surgery. Follow-up is generally carried out for 5 years, although some facilities continue to follow up their patients for 10 years. During the implementation of diagnostic imaging, many facilities add examination by interview, physical examination, and measurement of tumor markers.

Follow-up observation after definitive chemoradiotherapy

Although CT and esophageal endoscopy are usually employed for follow-up observation after definitive chemoradiotherapy, there have been no reports providing evidence for establishing the optimal frequency for such examinations or the duration of follow-up. In most cases, these examinations are performed at 3–4 weeks after the end of chemoradiotherapy and after the end of each course of additional chemotherapy. Thereafter, follow-up examinations are generally carried out every 3 months during the first year after therapy, and every 4–6 months from the second year onward after therapy. Residual carcinoma or recurrence after chemoradiotherapy is found frequently in the primary focus in the esophagus or in the regional lymph nodes, and in most cases recurrence occurs within 1–2 years after the start of therapy (see "Chemoradiotherapy").

After definitive chemoradiotherapy for esophageal carcinoma, observation for possible late adverse events related to radiotherapy such as radiation pneumonitis, pleural effusion, and pericardial effusion is necessary, in addition to examinations for recurrence. These aforementioned disorders may cause deterioration of a patient's QOL, and

radiotherapy-related late toxicity may even lead to death (see "Radiotherapy").

Surveillance for metachronous multiple esophageal carcinomas and multiple carcinomas arising from other organs

Esophageal carcinoma is relatively frequently accompanied by metachronous multiple esophageal carcinoma. In addition, the occurrence of metachronous carcinomas in other organs, such as gastric carcinoma and cancer of the head and neck region, is not rare. Metachronous carcinoma of other organs has been reported as the predominant cause of postoperative death in pN0 patients. 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 entire esophagus (remaining esophagus in resected cases) and the stomach regularly and carefully. Surveillance for the development of colorectal carcinoma or other carcinomas is also necessary.

Treatment of recurrent esophageal carcinoma

Summary

The initial treatment for esophageal carcinoma is selected from a wide variety of options, including endoscopic treatment, radical surgery, and definitive chemoradiotherapy. Therefore, treatment of recurrent esophageal carcinoma should be determined according to the modality selected for the initial treatment. In addition, treatment of recurrent carcinoma varies according to the type of recurrence, i.e., lymph node metastasis, local recurrence, distant organ metastasis, or the combination of these. The general condition of the patient at the time of recurrence also exerts influence on the selection of treatment. Recurrence is not rare even in patients in whom the initial treatment has been properly implemented. Large-scale clinical trials to clarify issues related to treatment of recurrence are difficult to conduct. Recurrent carcinoma may be curable depending on the type of recurrence, and aggressive treatment may be desirable. Treatment, however, is often aimed at suppression of tumor aggravation and improvement of the QOL.

Treatment of recurrence after endoscopic resection

Although local recurrence after endoscopic mucosal resection most often occurs within 1 year after the initial treatment, it may even occur after 2–3 years in some cases. In recent years, the indications for endoscopic resection have been extended from the aspect of clinical research. The indications and types of additional treatment after endoscopic resection are variable, and quite a number of patients are followed up without any additional treatment.

Treatment of recurrence after radical surgery

Recurrence after radical surgery has been reported to occur in 28–47 % of patients in Japan. Reports of recurrence rates of 50 % or more are not rare from Europe and North America. In relation to the mode of recurrence, lymph node or local recurrence is found in 22–68 % of patients, and distant organ metastasis in 12–51 % of patients; the two types of recurrences have been reported to occur in combination in 7–27 % of patients. Lymph node recurrence usually involves the cervical or superior mediastinal lymph nodes, and distant organ recurrence most frequently involves the lung, followed by the liver, bone and brain, in descending order of frequency. Metastasis to the small intestine or colon has also been reported.

The survival rate of patients with recurrence after radical resection of esophageal carcinoma is extremely poor, with the median survival time from the diagnosis of recurrence reported to be 5–10 months. However, long-surviving cases and cases of complete cure do exist; therefore, aggressive treatment is desirable.

Treatment of recurrence after radical resection of esophageal carcinoma is selected on the basis of the site, type, and extent of recurrence. Treatment also depends on the general condition of the patient at the time of recurrence, whether the recurrence is within or outside the scope of surgical manipulation, and whether or not the patient has received radiation pre- or postoperatively. Therefore, there is little data on the treatment results from a large number of patients with various clinical conditions.

Treatment of recurrence in cases showing CR after definitive chemoradiotherapy

It has become more common in recent years to adopt definitive chemoradiotherapy as the initial treatment, not only for cases of unresectable esophageal carcinoma, but also for those with resectable esophageal carcinoma. Although this therapy yields a relatively high rate of CR, recurrences, including local ones, are frequently seen (see "Chemoradiotherapy").

Palliative medicine

Summary

Although palliative care should be provided in all fields of cancer, a decrease in the patient's QOL is particularly common in patients with esophageal carcinoma, caused by the

difficulty in swallowing, malnutrition, and/or cough due to fistula formation. Consideration of procedures for symptom relief and maintenance and improvement of the QOL is required from the initial stages of treatment. However, selection of such procedures is currently left to the discretion of the treating institution. Close investigation of this issue would be desirable in the future. All health-care providers should acquire the basic knowledge and skills involved in the field of palliative medicine.

According to the WHO (2002), palliative care is defined as "an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." Palliative care should ideally begin when a patient is diagnosed as having cancer. This type of care is needed by all cancer patients and is provided in daily clinical practice. Palliative care requires a team approach that includes not only the doctors in charge and nurses, but also psycho-oncology specialists, pharmacists, social workers, and physical therapists. It has been pointed out that in particular, the role of a specialist nurse as a team leader is important in the palliative care of patients with esophageal carcinoma.

It is not rare, particularly in cases of esophageal carcinoma, that the patient has decreased QOL from the time of diagnosis because of difficulty in swallowing and malnutrition due to esophageal stenosis, cough due to mis-swallowing, or a fistula and chest pain due to the tumor. It is important to provide palliative care and treatment for the purpose of maintaining or improving QOL in parallel with the initial treatment that is aimed at cure of the disease.

Important issues in the palliative care of patients with end-stage esophageal carcinoma include difficulty in swallowing due to esophageal stenosis and the resultant malnutrition, the symptoms arising from airway stenosis and fistula formation to the airway, and cachexia and other symptoms due to distant metastasis and hypercalcemia. Among these, relief of symptoms arising from esophageal stenosis, airway stenosis, or fistula formation may be attempted by palliative treatments such as radiotherapy, chemoradiotherapy, esophageal stent insertion, airway stent insertion, and esophageal bypass (see "Radiotherapy" and "Chemoradiotherapy").

Gastrostomy or enterostomy as well as intravenous hyperalimentation may be performed to deal with malnutrition. These palliative treatments are typically employed for patients with esophageal carcinoma. Correct decisions as to the method and timing of implementation of these treatments are critical in the provision of palliative care for patients with end-stage esophageal carcinoma.

However, there have been few large-scale studies that have evaluated the efficacy and safety of various treatments and procedures in palliative medicine for patients with esophageal carcinoma. There have been no studies on the possibility of radiotherapy or chemotherapy providing survival advantage over best supportive care. However, it is a fact that in the actual clinical setting, a certain proportion of patients who have undergone these treatments have shown marked improvement in their QOL. Health-care providers should be skilled in palliative treatments and procedures specific to esophageal carcinoma, and the appropriate treatments should be employed proactively after obtaining informed consent from the patients.

In addition, health-care providers who are engaged in the treatment of esophageal carcinoma often encounter fatal conditions, such as acute respiratory arrest due to airway obstruction or massive hematemesis due to perforation into the aorta. In many cases, rescue of the patient is difficult once these events occur. It is important to give adequate explanation in advance about the possible occurrence of such events, particularly to the patients' families. Because the patients and their families have to live with the fear of sudden death or sudden change in clinical condition, provision of psychological support and mental care to both are indispensable. To treat carcinoma-related pain, procedures described in the Clinical Guideline for Pharmacological Management of Cancer Pain issued by the Japanese Society for Palliative Medicine are recommended.

Therapeutic efficacy and guidelines in Europe and North America: including the results of prognostic studies based on national registries

Summary

Unlike the situation in Japan, in Europe and North America, adenocarcinomas originating in the lower esophagus account for a large proportion of esophageal lesions. Therefore, the methods of treatment and their results are not necessarily comparable to those in Japan.

A simple comparison of endoscopic treatments in Japan and Western countries is precluded by differences in the criteria for selection of suitable candidates. There are no well-established guidelines.

Transhiatal esophagectomy is common, reflecting the increase in the frequency of lower esophageal adenocarcinoma. The extent of lymph node dissection is often restricted to the middle and lower mediastinum. Although there are no large differences from Japan in terms of surgical indications in relation to the disease stage, the surgical

results have not been satisfactory in Europe and North America.

The reported efficacy of neoadjuvant chemotherapy varies between Europe and North America. US Guidelines restrict neoadjuvant chemotherapy to carcinomas of the lower esophagus and the esophagogastric junction, and recommend neoadjuvant chemoradiotherapy for carcinoma arising in other parts of the esophagus. The England/Wales and Scotland, guidelines recommend 2 courses of neoadjuvant chemotherapy for cases with resectable disease, but do not recommend neoadjuvant chemoradiotherapy.

In regard to non-surgical treatment, as chemoradiotherapy has been shown to yield better results than radiation monotherapy; guidelines published in Europe and North America both recommend chemoradiotherapy as do those published in Japan.

There are differences in the epidemiology of esophageal carcinoma between Japan and Europe/North America, which make it impractical to simply compare the methods and results of treatment between these regions. In regard to the histologic type, squamous cell carcinoma accounts for more than 90 % of all cases of esophageal carcinoma in Japan, whereas adenocarcinoma accounts for more than 50 %, and squamous cell carcinoma for less than 40 % of cases in Europe and North America. As for the location of the tumor, tumors arising in the middle thoracic esophagus are reported as the most frequent, accounting for more than 50 % of all cases in Japan, whereas lesions arising in the lower thoracic esophagus are reported to account for more than 50 % of the cases in Europe and North America. The past two decades have seen an increase in the frequency of adenocarcinoma in Western countries, and it is reported that Barrett's esophagus developing from obesity and GERD have been reported as background factors for this increase. Therefore, these factors account for the differences in therapeutic strategies and treatment results between Japan and the US/Europe.

Guidelines for the diagnosis and treatment of esophageal carcinoma have also been published in some Western countries. These include 4 comprehensive guidelines, i.e., 2 guidelines from the USA, 1 from the UK, and another from Scotland. In the USA, Physician Data Query (PDQ) from the National Cancer Institute (NCI) and information from the National Comprehensive Cancer Network (NCCN) are available on the Internet, and the information is updated continually, with data added from the latest literature. In particular, the NCCN guidelines provide an algorithm to facilitate selection of the appropriate treatment. The strength of recommendation is categorized according to the level of evidence. In the guidelines published in England/Wales and Scotland, the levels of evidence are specified as in the Japanese guidelines. They provide specific information on the epidemiology and pathogenesis, perioperative management, and postoperative complications as well as on the palliative treatment of esophageal carcinoma.

Endoscopic treatment

Although there are reviews on endoscopic treatment from Europe and North America, they differ from reports published in Japan in those cases of high-grade dysplasia are included as target lesions, and photodynamic therapy (PDT) is also included as a type of treatment. Therefore, a simple comparison with reports from Japan is not possible. The reported 5-year survival rate after EMR is 87.7 % in Japan, according to the national statistics published in 2002.

It is rare in Western countries for esophageal carcinoma to be detected at an early stage; therefore, EMR is not commonly performed. Therefore, guidelines regarding endoscopic treatment are limited. Although the NCCN guidelines recommend EMR for mucosal carcinoma (Tis or T1a), the NCI guidelines recommend surgery for Stage 0 lesions. In the Scottish guidelines, EMR is recommended for carcinomas confined to the mucosal layer. The England/Wales guidelines contain no description of endoscopic resection.

Surgery

In the USA, transhiatal esophagectomy without thoracotomy is regarded as the standard surgical treatment technique for esophageal carcinoma for the following reasons: the results of resection are poor due to the prevalence of advanced carcinoma; surgical complications are frequent because of the high rate of high risk patients; carcinoma in the lower esophagus is frequent; no difference in the recurrence-free survival has been reported between transhiatal esophagectomy and subtotal esophagectomy via right thoracotomy accompanied by lymph node dissection and complications are less frequent with the former procedure. The extent of lymph node dissection is often restricted to the middle and lower mediastinum, and dissection covering all the three regions (cervical, thoracic, and abdominal) is not generally performed. Table 7 shows the results of randomized controlled trials of surgical treatment of esophageal carcinoma reported in and after 1990, and the 2002 Japanese national registry data. Although there are variations in the stages considered for resection among overseas studies, the reported 5-year survival rate is generally about 25 % or less, being significantly different from the corresponding rate of 44.1 % in all cases treated by resection in Japan.

According to the NCCN guidelines, surgery is indicated for Stage 0-III or resectable Stage IVA carcinoma of the esophagus. As for cases of cervical esophageal carcinoma, the NCCN guidelines state that definitive

Table 7 *Summary of randomized controlled trials of surgical treatment for esophageal carcinoma and national registry data of the Japan Esophageal Society*

Author	Year	Target[a]	Treatment	No. of cases	Histologic type S/A/O	Resected cases	Treatment-related deaths	2-year survival (%)	3-year survival (%)	5-year survival (%)	MST (month)
Bosset	1989–1995	Stage I–III, excluding T3N1	S	139	134/0/5	137	5 (3.6 %)	About 42	About 35	About 25	18.6
			CR + S	143	139/0/4	138	17 + 1 (12.6 %)	About 48	About 35	About 25	18.6
Kelsen	1990–1995	Stage I–III	S	234	110/124	217	13 (5.6 %)	35	19	7	16.1
			C + S	233	103/120	171	5 + 10 (6.4 %)	31	18	6	14.9
MRCOCWP	1992–1998	Resectable cases	S	402	124/268/10	386	40 (10 %)	34	About 25	About 15	13.3
			C + S	400	123/265/12	361	36 + 8 (11 %)	43	About 32	About 25	16.8
Bedenne	1993–2000	T3N0-1M0 (Stage II–III) ditto CR cases	CR + S	129	115/14	107	12 (9.3 %)	39.9			16.4
			CR + C	130	115/15	1	1 (0.8 %)	35.4			14.9
Burmiester	1994–2000	Stage I–III, excluding T4	S	128	50/78/0	110	6 (5.4 %)	39.8	28.1	14.8	19.3
			CR + S	128	45/80/3	105	5 (4.7 %)	45.3	32.8	16.4	22.2
Stahl	1994–2001	T3-4N0-1M0	S	86	86/0	51	11 (12.8 %)	39.9	31.3		16.4
			CR + S	86	86/0	0	3 (3.5 %)	35.4	24.4		14.9
Japan Esophageal Society	2002	All resected cases	S + α			1518	41 (4.5 %)[b]	62.2	53.6	44.1	About 44
		Stage I	S + α			361		88.5	82.7	71.2	About 53
		Stage IIA	S + α			290		66.6	60.7	49.2	About 46
		Stage IIB	S + α			211		64.9	55.7	42.8	About 20
		Stage III	S + α			494		44.4	33.7	27.7	

S Surgery, *C* chemotherapy, *R* radiotherapy, +α regardless of whether or not adjuvant therapy was given, *S* squamous cell carcinoma, *A* adenocarcinoma, *O* other histologic type, *MST* Median survival time

[a] Clinical TNM classification

[b] In-hospital mortality (including direct surgical death and death from recurrence)

chemoradiotherapy should be administered for carcinomas in this region and those located less than 5 cm from the cricopharynx, with no consideration of surgery.

Preoperative and postoperative adjuvant therapy

Preoperative adjuvant therapy A meta-analysis of several randomized controlled trials performed in Europe and North America to examine the usefulness of neoadjuvant chemotherapy revealed no consistent benefit of neoadjuvant chemotherapy on survival. Thus, the efficacy of neoadjuvant chemotherapy for patients with resectable disease (T1-3N0, 1M0, UICC classification, 2002 edition) remains unclear. In addition, a meta-analysis reported in Australia in 2007 concluded that neoadjuvant chemoradiotherapy may have additional benefit in cases of esophageal adenocarcinoma, but is not effective for patients with squamous cell carcinoma, emphasizing the need to choose adjuvant therapy according to the histologic type of the disease.

According to the NCCN guidelines, preoperative therapy is indicated for cases with T1b, N1, T2 to resectable T4, and resectable Stage IVA disease. Neoadjuvant chemotherapy is restricted to cases of adenocarcinoma located in the lower esophagus or the esophagogastric junction. Lesions in other parts of the esophagus are described as indications for neoadjuvant chemoradiotherapy, with the recommended drugs specified by category. The England/Wales and Scotland guidelines do not recommend neoadjuvant chemoradiotherapy, although they state that adjuvant chemotherapy with 2 courses of cisplatin + 5-FU should be considered for cases with resectable disease.

Postoperative adjuvant therapy The NCCN guidelines recommend postoperative chemotherapy only for patients who have received neoadjuvant chemotherapy. Chemoradiotherapy is recommended for T2-3N0-1 adenocarcinoma or N1 adenocarcinoma cases with R0 resection. Some R1–2 cases may also be included. The Scottish guidelines do not recommend either postoperative chemotherapy or chemoradiotherapy, based on the results of randomized controlled trials for the former and the lack of data for the latter. The England/Wales guidelines also do not recommend postoperative chemotherapy.

Chemoradiotherapy

With regard to non-surgical treatment, conventional guidelines recommend the use of chemoradiotherapy, based on reports that chemoradiotherapy yielded better results when concurrent chemoradiotherapy was compared with radiation monotherapy. According to the 2002 national registry of the Japan Esophageal Society, the 5-year survival rate was 15.1 % in patients who received radiation monotherapy, whereas it was 22.9 % in those treated by chemoradiotherapy. The corresponding rates by disease stage were 32.5 vs. 52.0 % for Stage I–IIA cases and 4.2 vs. 14.9 % for Stage IIB-IVB cases, indicating the superiority of chemoradiotherapy over radiation monotherapy. The protocol recommended by the Radiation Therapy Oncology Group that is commonly employed in Europe and North America consists of irradiation using the multiple field technique at a total dose of 50.4 Gy administered in 28 fractions, with the exposure field covering the region within 5 cm above and below the tumor. This regimen is based on the results of a randomized controlled trial that found no difference in the survival period between standard-dose (50.4 Gy) and high-dose (64.8 Gy) chemoradiotherapy, and reached a negative conclusion about the benefit of increasing the total radiation dose. The NCCN guidelines specify that the radiation dose should be 50–50.4 Gy.

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Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This article does not contain any studies with human or animal subjects performed by any author(s).

Conflict of interest Funds to support the development of these guidelines were provided by the Japan Esophageal Society and the Ministry of Health, Labour and Welfare Scientific Research (Study on the appropriate development and publication of guidelines for the diagnosis and treatment while maintaining full disclosure: Hirata's study group). Prof. Kitagawa has received grants from Taiho Pharmaceutical CO., LTD., Chugai Pharmaceutical CO., LTD., Kyowa Hakko Kirin CO., LTD., Merck Serono CO., LTD., Ono Pharmaceutical CO., LTD., Novartis Pharma CO., LTD., Yakult Honsha CO., LTD., Bristol-Myers Squibb Daiichi Sankyo CO., LTD., Shionogi CO., LTD., Terumo Corporation, Torii Pharmaceutical Co., Ltd., AstraZeneca CO., LTD. Other authors have no conflict of interest to declare with profit making or nonprofit organizations or providers of medical products and medical supplies. The Ethics Committee and Administrative Board of the Japan Esophageal Society required members of the Committee to Develop Guidelines for the Treatment of Carcinoma of the Esophagus and the Guideline Evaluation Committee to self-report any potential conflict of interest.

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ORIGINAL ARTICLE

Relationship between functional end-to-end anastomosis for colon cancer and surgical site infections

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Abstract
Purpose Surgical site infections (SSI) are a common complication of gastrointestinal tract surgery. In this study, we explored the correlation between the anastomosis method and the incidence of SSI.
Methods A total of 110 patients underwent ileocecal resection or right hemicolectomy for the excision of colon cancer. Two methods (open and closed, 28 and 82 patients, respectively) of functional end-to-end anastomosis were adopted.
Results Increased perioperative blood loss ($p = 0.029214$), a longer hospital stay ($p = 0.026668$) and the development of SSI ($p = 0.000181$) were significantly correlated with the open method. There was no correlation between SSI and the body mass index, or between SSI and the length of the surgery or diabetes mellitus. However, patients that developed SSI tended to be obese.
Conclusion The open method was associated with a higher incidence of SSI. Therefore, it is necessary to consider potential contamination of the surgical field at the time of anastomosis to reduce the incidence of SSI.

Keywords Functional end-to-end anastomosis · Colon cancer · Surgical site infection

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Introduction

Of the many anastomosis techniques that have been described, functional end-to-end anastomosis (FEEA) is relatively straight forward and safe, being associated with less leakage than hand-sewn anastomosis [1], and functioning in a similar manner to end-to-end anastomosis. However, several problems persist with this type of anastomoses. For example, bleeding from the anastomotic line reportedly occurs in 1.6–5 % of the cases [2, 3], and postoperative anastomotic stenosis has also been identified as a major complication of FEEA [4], which may be related to the additional suture techniques being applied to the first suture edge and the anastomotic circumference [5]. Furthermore, surgical site infections (SSI) are a significant complication of gastrointestinal tract surgery, particularly colon cancer surgery. Although surgeons always perform such procedures with the utmost care, SSI cannot be completely prevented. In the present study, we explored the correlation between the anastomosis methods and the incidence of SSI.

Materials and methods

The medical records of patients who underwent FEEA between June 2009 and October 2012 were retrospectively reviewed. These patients underwent either ileocecal resection or right hemicolectomy for the excision of the cecum, ascending colon or transverse colon. Although the anastomoses during laparoscopic surgery were performed outside of the body at our department, laparoscopic surgery was excluded from this study, because laparoscopic and open surgeries are performed on very different backgrounds. A total of 110 patients underwent FEEA by either the open

Table 1 Anastomotic methods and characteristics of each surgical stapler

Method	Closed method	Open method
Device	Endo GIA universal	PROXIMATE linear cutter
Length of the cartridge	60 mm	75 mm
Number of the cartridges used during FEEA	4	2
Contamination at the exchange of the cartridge	Possible	Confirmed

or closed method. From December 2011 to August 2012, we adopted the open anastomotic method for economic reasons. There was no case selection during this period. All patients received antibiotic prophylaxis and mechanical bowel preparation, and all patients were treated using a wound protector (ALEXIS®) during the operation.

We herein investigated the correlations between these methods and the incidence of SSI.

The FEEA maneuver

Of the 110 patients who underwent FEEA, 82 were treated by the closed method and 28 were treated by the open method. In the closed method, the ileum and colon were separated using a linear stapler equipped with a cutting knife (Endo GIA Universal 60-4.8; Covidien). Small holes were made in the walls of the ileum and colon using an electronic scalpel. Another stapler was then inserted into these holes to perform the side-to-side anastomosis. Finally, the holes were resected using another stapler. The stapled edge and parts of the double-stapled edge were reinforced with 4–0 vicryl sutures (Ethicon Inc., Somerville, New Jersey). We used four cartridges for this method. For the open method, the bowel was resected with a knife. A linear knife (Proximate Linear Cutter, blue, 75 mm; Ethicon Endo-Surgery, Cincinnati, Ohio) was inserted into the colon and ileum to perform the side-to-side anastomosis. Finally, the intestinal tract stump was closed using another stapler. The stapled edge and portions of the double-stapled edge were reinforced using 4–0 vicryl sutures (Ethicon Inc., Somerville, New Jersey). Two cartridges were used for this method.

The characteristics of each surgical stapler are shown in Table 1 and Fig. 1 illustrates how the cartridges were changed. There was a lower contamination risk at the time of cartridge exchange using the Endo GIA Universal stapler compared with using the Proximate Linear Cutter.

Wound infection

Surgical site infections (SSI) were identified based on the standardized criteria [6–8]. We evaluated incisional (superficial or deep) infections postoperatively; however, these infections did not involve abscesses due to sutures, or skin rubor due to exudate fluid or fat dissolution. In cases where the wound was not dry, we estimated the extent of infection.

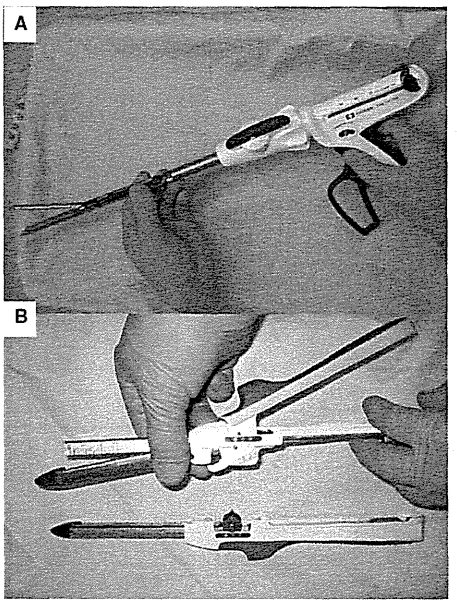

Fig. 1 Cartridge exchange methods. **a** Endo GIA Universal 60-4.8 (COVIDIEN) was used for the closed method. **b** Proximate Linear Cutter, blue, 75 mm (Ethicon Endo-Surgery) was used for the open method

Statistical analysis

Correlations between the patient characteristics, method of anastomosis and wound infection were assessed using the χ^2 test and Student's t test.

Results

Between June 2009 and October 2012, a total of 110 patients underwent ileocecal resection or right hemicolectomy for

Table 2 Characteristics of the patients for each anastomosis method

	Closed method	Open method	*p* values
n	82	28	
Gender			
Male	37	16	N.S.
Female	45	12	
Age (average in years)	72.9	74	N.S.
Operation			
Ileocecal resection	48	17	N.S.
Right hemicolectomy	34	11	
Stage			
0	0	1	N.S.
1	25	4	
2	34	15	
3a	12	4	
3b	11	3	
4	0	1	
BMI	21.4	29.4	N.S.
Perioperative blood loss (mL)	46.2	73.5	0.029214
Duration of the operation (min)	79.6	82.1	N.S.
Length of hospital stay (days)	18.8	23.9	0.026668
Number of cases with SSI	9	15	0.000181

N.S. not significant

Table 3 Patient characteristics and the incidence of SSI

	SSI−	SSI+	*p* values
n	81	24	
BMI	21.6	33.5	N.S.
DM	9 (11.1 %)	3 (12.5 %)	N.S.
Perioperative blood loss (mL)	49.7	81.3	0.01888
Duration of operation (min)	81	80.5	N.S.
Length of hospital stay (days)	18.5	27.7	0.00038
FEEA			
Open method	9	15	$p < 0.001$
Closed method	72	9	

N.S. not significant

the excision of the cecum, ascending colon or transverse colon. No anastomotic leakage occurred in these cases. The median patient age was 73.4 years (age range 52–96 years), the male/female ratio was 53/57 and the median body mass index (BMI) was 25.4 kg/m^2 (range 15.9–31.1 kg/m^2).

The characteristics of the patients and anastomosis methods are shown in Table 2. The closed method was performed for 82 patients and the open method was performed for 28. There were no significant differences in the staging between the closed and open groups. However, there were significant differences between the closed and open methods with regard to perioperative blood loss (46.2 vs. 73.5 mL, $p = 0.029214$), the length of hospital stay (18.8 vs. 23.9 days, $p = 0.026668$) and the incidence of SSI (9 vs. 15 cases, $p = 0.000181$). There was no significant difference in length of the surgery between the two anastomotic methods. Patients treated by the open method had slightly higher BMI values, but there was no significant correlation between the BMI and surgical method.

The factors associated with SSI are shown in Table 3. The amount of perioperative blood loss and the anastomosis method significantly influenced the incidence of SSI. The mean perioperative blood loss of cases with and without SSI was 81.3 and 49.7 mL, respectively ($p = 0.01888$). The open FEEA method was significantly correlated with an increased incidence of SSI ($p < 0.001$). In cases with SSIs, the length of hospital stay was increased. There were no correlations between SSI and the BMI or length of the surgery. However, the patients who developed SSI tended to be obese compared with those who did not (BMI, 33.5 vs. 21.6 kg/m^2, respectively; $p = 0.05858$). Three out of the 24 patients (12.5 %) with SSI were diabetic, and so were 9/81 (11.1 %) cases without SSI. No correlation existed between SSI and DM. All diabetic patients had controlled glucose levels by oral anti-diabetic agents.

Discussion

Many automatic anastomotic techniques have been employed in gastrointestinal surgery [5, 9–11]. One of these techniques, FEEA, has gained wide recognition because of its practicability and safety [10–12]. There are two primary FEEA methods, and each has unique advantages and disadvantages. Conventionally, we have performed FEEA by the closed method. From December 2011 to August 2012, we adopted the open anastomotic method, assuming at the time that it was more economical. The Endo GIA Universal stapler was used for the closed method with four 60-mm cartridges. For the open FEEA method, the Proximate Linear Cutter with two 70-mm cartridges was used. The difference in cost between these two methods was largely based on the number of cartridges, but this was not the only difference. There is a possibility of contamination at the time of cartridge exchange using the Proximate Linear Cutter, thus increasing the risk of intraoperative SSI. Nonetheless, the FEEA method can reduce the risk of intraoperative bacterial contamination compared with the hand-sewn procedure, because the mucosal surface during the FEEA procedure is exposed for a shorter period of time [13].

In FEEA, the length of exposure of the mucosal surface is dependent on the anastomosis technique used. In the

open method, the exposure of the mucosal surface is greatly increased compared with that in the closed method. After switching to the open method, the incidence of wound infections increased. However, washing the potentially contaminated portion of the device and implementing a glove exchange at the time of cartridge exchange decreased the incidence of SSI. Hence, through careful operations and increased awareness of the risk of bacterial contamination, the rate of SSI decreased to 11.5 % (3/26 cases) in our department for the open method.

In the open method, the perioperative blood loss was significantly increased compared with that in the patients treated using the closed method. SSI was also significantly associated with increased perioperative blood loss. Hagihara et al. [14] reported that intraoperative blood loss and a longer surgery were associated with an increased incidence of SSI. In our case, the duration of surgery was almost identical for the open and closed methods. Although the risk of SSI may not be influenced by the relatively short surgical procedures, such as in those commonly used for the treatment of colon cancer, some studies have shown that the BMI or DM is also significantly associated with the development SSI [15–19]. In this study, although there was no significant correlation between the BMI and SSI, the patients who developed SSIs tended to have higher BMIs. The diabetic patients included in the present study might not have had an increased risk of SSI because of their well-controlled glucose levels.

The development of SSI was associated with a significantly longer hospitalization period. The open FEEA method was adopted by our institute to minimize the expense of medical materials, but the length of hospitalization increased as a result, thereby also increasing the overall costs.

In conclusion, the incidence of SSI was related to the anastomosis method used for colon cancer surgery. The open FEEA method was associated with a greater incidence of SSI. The individual physical characteristics of the devices may also affect contamination; therefore, it is necessary to carefully consider the possible infection of the surgical field at the time of anastomosis.

Conflict of interest Hitoshi Ojima and co-authors have no conflicts of interest.

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ORIGINAL ARTICLE

Nesfatin-1 Suppresses Gastric Contractions and Inhibits Interdigestive Migrating Contractions in Conscious Dogs

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Abstract
Background Nesfatin-1 is a novel 82-amino acid anorectic peptide. Acute injection of nesfatin-1 into the third brain ventricle reduces food consumption during the dark phase in rats. Nesfatin-1 is also expressed in gastric X/A-like cells in the peripheral tissues. Nesfatin-1 has been reported to reduce gastric and duodenal motility and to delay gastric emptying.
Aim In the present study, we investigated the effects of nesfatin-1 on gastrointestinal motility in conscious dogs.
Methods Force transducers were implanted onto the serosal surfaces of the gastric bodies, gastric antra, duodena, and jejuna of healthy beagle dogs, and gastrointestinal motility was monitored. We evaluated the effects of nesfatin-1 on gastrointestinal motility and on the circulating levels of nesfatin-1 in the fasted and fed states.
Results The intravenous administration of nesfatin-1 reduced gastric contractions and inhibited cyclical interdigestive migrating contractions in the fasted state. In the fasted state, circulating levels of nesfatin-1 tended to increase during late phase I. In addition, the kinetics of the circulating levels of nesfatin-1 were opposite to those of ghrelin during the fasted state.
Conclusions Nesfatin-1 regulates gastrointestinal motility, and, in particular, it inhibits gastric contractions in the fasted state. Interdigestive migrating contractions may be regulated by interactions between nesfatin-1, ghrelin, and motilin.

Keywords Nesfatin-1 · Ghrelin · Motilin · Gastrointestinal motility · Interdigestive migrating contractions

Abbreviations

IMCs	Interdigestive migrating contractions
MI	Motility index
NUCB2	Nucleobindin-2

Introduction

Nesfatin-1, which was discovered by Oh et al. in 2006, is an 82-amino acid peptide derived from the precursor nucleobindin-2 (NUCB2) [1]. Nesfatin-1 is expressed in the hypothalamic area of the brain, including the paraventricular nucleus, arcuate nucleus, supraoptic nucleus, lateral hypothalamic area, and zona incerta. The intracerebroventricular administration of nesfatin-1 inhibits food intakes dose-dependently for 6 h during the dark phase in rats. Other studies have reported the anorectic effects of nesfatin-1. Moreover, Stengel et al. [2] reported that the intracerebroventricular administration of nesfatin-1 reduces gastric emptying in rats. In the peripheral tissues, nesfatin-1 and NUCB2 are located in the gastric X/A-like endocrine

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cells [3]. Nesfatin-1 and ghrelin reportedly coexist in the gastric X/A-like cells. The intraperitoneal administration of nesfatin-1 also inhibits food intakes dose-dependently in mice [4]. Although it has been hypothesized that peripheral nesfatin-1 acts through the vagus nerve [5, 6] and the blood–brain barrier [7, 8], the detailed pathways underlying its action are unclear at present.

Feeding behaviors, gastrointestinal hormones, and gastrointestinal motility are closely associated [9, 10]. Atsuchi et al. [11] reported that the intracerebroventricular administration of nesfatin-1 suppresses gastric–duodenal contractions in rats in the fed state. Furthermore, Li et al. [12] reported that the intracerebroventricular administration of nesfatin-1 suppresses gastric contractions in anesthetized rats. Currently, however, there are no other publications that describe the relationship between nesfatin-1 and gastrointestinal motility. We previously designed an experimental system to monitor gastrointestinal contractions in conscious dogs, and we have published reports from studies that have investigated the relationships between gastrointestinal hormones and gastrointestinal motility. These have included studies on xenin and gallbladder contractions [13], ghrelin and gastrointestinal motility [14], and motilin and interdigestive migrating contractions (IMCs), which are the cyclical motor contractions that characterize gastrointestinal motility during fasting. In dogs and humans, IMCs are regulated by motilin and ghrelin [15].

In this study, we used our experimental model of gastrointestinal motility in conscious dogs to investigate the effects of the intravenous administration of nesfatin-1 on gastrointestinal contractions and the relationships between blood nesfatin-1 concentrations and gastrointestinal motility.

Methods

Animal Preparation

The experiments were conducted in five healthy conscious dogs of either sex, each weighing 10–12 kg. The procedures were approved by the Review Committee on Animal Use at Gunma University, Maebashi, Japan. Overnight-fasted dogs were anesthetized using a single intravenous injection of thiopental sodium (20 mg/kg body weight) (Ravonal; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), and general anesthesia was maintained using intratracheal halothane inhalation (Fluothane; Takeda Pharmaceutical Company Limited, Osaka, Japan) and oxygen. A silastic tube (Silastic 602–205; Dow Corning, Midland, MI, USA) was inserted into the inferior vena cava through the left femoral vein branch. The abdominal cavity was opened, and four force transducers (F-12 IS; Star Medical, Inc., Tokyo, Japan) were implanted on the serosal surfaces of the gastric body, antrum, duodenum, and jejunum (30 cm distal to the ligament of Treitz). Wires from each force transducer were tunneled subcutaneously to the dorsum and connected to an eight-channel telemeter (GTS-800; Star Medical, Inc., Tokyo, Japan); hence, gastrointestinal activities were continuously recorded on a computer (Adif1412.dill; Star Medical, Inc., Tokyo, Japan).

After the operation, the dogs were housed in individual experimental cages. The dogs were fasted for 2 days following the operations, and they were maintained by intravenous infusions of Lactec G (Otsuka Pharmaceutical Co., Tokyo, Japan) at daily volumes of 500 mL. cefmetazole (1 g) was administered intravenously, once preoperatively, and once on the first day after the operation. The dogs were allowed to recover for $\geq$14 days. The animals were fed standard dog food (20 g/kg) (Funabashi Farm, Funabashi, Japan) once daily and given water ad libitum.

Once all of the experiments had been completed, the dogs were killed using an overdose of thiopental sodium and potassium chloride.

Fasted Gastrointestinal Motility and Nesfatin-1 Administration

Five dogs were used for the experiments. These experiments were initiated after confirmation of the regular occurrence of gastric phase III contractions. Generally, gastric phase III contractions were restored approximately 14 days after the operation. We intravenously administered saline or nesfatin-1 (Recombinant Human Nucleobindin-2; ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA) at doses of 10, 30, or 100 μg/body, as slow single-bolus injections 1 h after the termination of spontaneous phase III contractions of the antrum. The gastrointestinal motility was subsequently recorded for over 2 h. The animals were assessed on different days.

Motility Index Analysis

Gastrointestinal motility was quantified by calculating the motility index (MI) that was equivalent to the area under the curve. The MI was calculated using a computer-assisted system (Eight Star System, version 6.0; Star Medical, Inc., Tokyo, Japan). The levels of fasting gastrointestinal motility were analyzed for 120 min following the injections of saline or nesfatin-1. The investigator who conducted the MI analysis was blinded in relation to whether the animal had been administered saline or nesfatin-1, and, hence, in the case of the latter, the dose at which nesfatin-1 was administered. The MI generated from each nesfatin-1 dose injected was compared with the MI generated from the injections of the control solution. Three MI assessments were undertaken per dog, and the mean value was used in

the statistical analyses. All data are expressed as the mean ± standard errors (SE). The data were subjected to detailed statistical analyses using an analysis of variance, followed by analysis using Fisher's protected least significant difference method. Values of $p < 0.05$ were considered statistically significant.

Fed Gastrointestinal Motility and Nesfatin-1 Administration

Five dogs were fed 20 g/kg of dog food (Cainz Dog Meal; Cainz Inc., Takasaki, Japan) after the spontaneous phase III contractions had terminated, and nesfatin-1 at doses of 10, 30, or 100 μg/body was administered intravenously 1 h after the animals were fed. The gastrointestinal motility was subsequently recorded for over 2 h.

Measurements of Nesfatin-1, Ghrelin, and Motilin

Whole blood samples were collected from the fasting animals from a central venous catheter, with sample collection beginning after the first or second phase III contractions of the day. Blood sampling was repeated at 20–30-min intervals. When the animals were in the fed state, blood was withdrawn at 0, 5, 15, 30, 60, and 90 min after feeding.

The blood samples were transferred into chilled tubes containing ethylenediaminetetraacetic acid-2Na and 500 U apoprotein, and they were centrifuged at 4 °C at 3,000×*g*. Two plasma samples, one for nesfatin-1 and motilin measurements and the other for ghrelin measurements, were immediately collected. To measure ghrelin levels using an enzyme-linked immunosorbent assay (ELISA), 0.1 mL of 1-N hydrochloric acid/mL plasma was added to the sample. All plasma samples were stored at −80 °C until the hormone analyses were conducted.

The nesfatin-1 concentrations in the plasma were measured using a nesfatin-1 ELISA kit (Shibayagi, Gunma, Japan). Although this kit was designed to measure concentrations of human nesfatin-1, human nesfatin-1 and dog nesfatin-1 have a 95 % amino acid homology. We therefore used this ELISA kit to evaluate plasma nesfatin-1 concentrations.

The ghrelin concentrations in the plasma were measured using the active ghrelin ELISA kit (Mitsubishi Kagaku

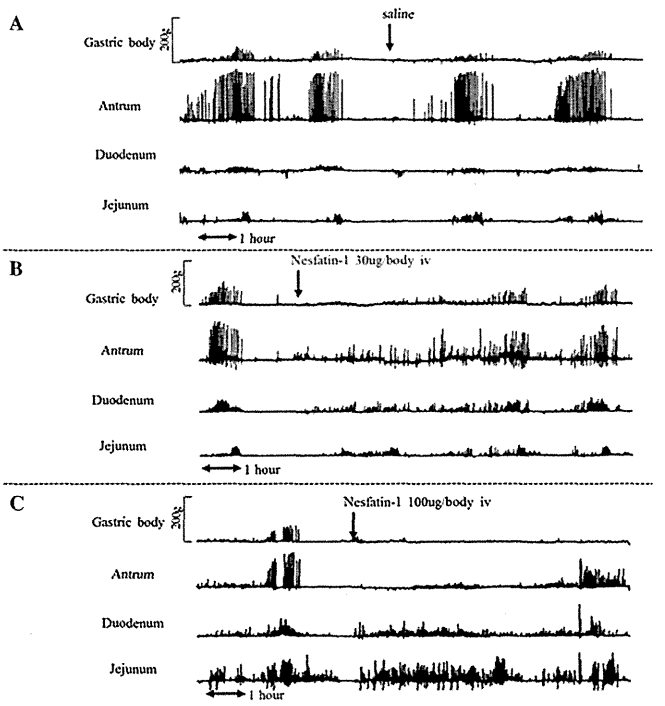

Fig. 1 Examples of the effects of intravenous injections of nesfatin-1/nucleobindin-2 on myoelectrical activity measured in the gastric body, antrum, duodenum, and jejunum of a conscious dog in the fasted state. **a** The control solution (saline) did not alter the intervals and amplitudes of the gastrointestinal contractions. **b** Nesfatin-1 (30 μg/body) reduced gastric contractions and inhibited interdigestive migrating contractions (IMCs). **c** Nesfatin-1 (100 μg/body) also reduced gastric contractions and inhibited IMCs