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ORIGINAL ARTICLE

Clinical significance of muscle layer interruption in T3 esophageal cancer

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Abstract
Background Patients with adventitia-invading (T3) tumors, which account for the majority of esophageal cancers, are indicated for surgery but still have a poor prognosis. Subclassifying T3 tumors based on clinical outcome would be useful for selecting adequate adjuvant therapies.
Methods Using 268 esophageal cancer specimens from patients without preoperative treatment, the length of the vertical and longitudinal tumor invasion, entire esophageal wall thickness, and interruption of the outer muscle layer were measured. These morphological parameters correlated with clinico-pathological factors and outcome.
Results Patients were classified as T1 (38.4 %), T2 (11.9 %), T3 (38.4 %), and T4 (11.2 %) and T stage correlated well with the four morphological parameters ($p < 0.0001$). Each of the four morphological parameters was a significant prognostic factor. A cutoff at 20 mm of muscle layer interruption (MLI) yielded the highest prognostic significance (5-year survival 36.7 vs. 59.1 %, $p = 0.009$). T3 tumors with <20 mm MLI showed survival rates equivalent to T2 tumors (5-year survival 59.5 %), whereas those with ≥20 mm MLI had survival rates similar to T4 tumors (5-year survival 26.7 %). Although lymphatic and hematogenic recurrence was not significantly different, local recurrences occurred more frequently in patients with T3 tumors with ≥20 mm MLI than in those with <20 mm MLI (4.3 vs. 21.4 %, $p = 0.019$).
Conclusions T3 esophageal cancer can be classified into subgroups according to the length of MLI. Additional local treatment would be indicated for T3 tumors with >20 mm MLI.

Keywords Muscle layer interruption · T3 · Esophageal cancer

Abbreviations
MLI Muscle layer interruption

Introduction

Esophageal cancer is one of the most common malignant neoplasms. Esophageal cancer ranks eighth in incidence and sixth in cancer deaths worldwide [1–4]. Recent advances in diagnostic modalities such as endoscopy enable us to detect esophageal cancer at earlier stages than before [5, 6], but advanced stage esophageal cancer is still often found at the time of diagnosis [7].

According to the TNM staging system, pathological T stage in esophageal cancer has traditionally been classified as T1, T2, T3, and T4 for many years [8]. However, in the new classification system in the seventh edition of TNM staging [9], T4 is subclassified into two groups. While T4a

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is classified as esophageal cancer invading an adjacent organ that is potentially resectable such as pleura and pericardium, T4b is classified as esophageal cancer invading an adjacent organ that is likely to be unresectable such as the trachea and aorta. These classifications are well known to reflect the incidence of lymph node metastasis and patient survival [10].

T3 esophageal cancer is defined as a tumor invading the adventitia and accounts for the majority of esophageal cancers. T3 tumors account for 46 % of esophageal cancers that are surgically resected, and reach 69 % excluding superficial esophageal cancer (T1) [11, 12]. However, T3 tumors are not subclassified by clinical outcome. T3 tumor stage covers a spectrum encompassing minimal invasion beyond the muscle propria to gross invasion to the adventitia just before an adjacent organ. T3 tumors can be removal macroscopically by surgery; however, microscopic residual tumor cells around cancer nests are possible, leading to local tumor recurrence. Therefore, it is very important to identify the subpopulation patients with T3 tumors who are at high risk of local recurrence, for which additional local treatment such as chemoradiotherapy should be considered. In this study, we measured several morphological aspects of the tumor in the surgical specimen and graded T3 tumors using these objective parameters. Finally, we were able to successfully subclassify T3 esophageal cancers in a way that adequately reflected the clinical outcome.

Methods

Patients and treatment

This retrospective study included 268 patients with thoracic esophageal cancers who underwent primary surgical resection without preoperative treatment between 1995 and 2010 at two institutions; the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, and Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.

The standard operation consisted of subtotal esophagectomy with 2 or 3 field lymph node dissections via right thoracotomy, and reconstruction using gastric tube, jejunum, or colon when the stomach could not be used. After hospital discharge, patients were seen every 2 months for the first 2 years then every 3 months thereafter. A CT scan of the neck, thorax, and upper abdomen was performed every 4 months for the first 2 years then every 6 months thereafter. Upper gastrointestinal endoscopy was performed annually. Recurrence was confirmed by CT scan and, if necessary, PET scan. Postoperative adjuvant chemotherapy consisting of cisplatin and 5-fluorouracil was indicated when lymph node metastasis was confirmed by pathological examination; however, postoperative chemotherapy was not given when the patient's postoperative systemic condition was poor. The median follow-up period for all patients was 27.2 months.

Pathological evaluation

All esophagectomy specimens were opened along their longitudinal axis from proximal to distal extending along the greater curvature of the stomach. All specimens were appropriately stretched and pinned, and fixed in formalin for at least 24 h. After fixation, the specimen was sliced longitudinally at 4-mm intervals. All parts of the main tumor were sliced and embedded in paraffin. Sections of 4-mm thickness were cut from the paraffin-embedded block and stained with hematoxylin and eosin.

All pathological examinations were done independently by two observers (K.S. and E.M.) who were blinded to patient outcome and other clinical findings. The descriptions of the tumor (appearance, invasion depth, histological type, and differentiation) and the lymph nodes (number in each station) were recorded. The pathological tumor stage was determined according to the seventh TNM classification system [9].

Measurement of morphological parameters

Longitudinal sections taken from the tumor center were utilized to measure the morphological parameters. The loupe image of the HE-stained slides was scanned with the computer through NanoZoomer 2.0HT (HAMAMATSU, Japan). Four pathological tumor-specific lengths were measured on NanoZoomer Digital Photography view software (HAMAMATSU, Japan) (Fig. 1).

As the vertical parameters of the tumor, the depth of tumor invasion and esophageal wall thickness were measured. Depth of tumor invasion was defined as the length from the superficial side of the tumor to the invasive front of the tumor. Esophageal wall thickness was defined as the length from the luminal side of the esophageal wall to the outer side of the esophageal wall. As the horizontal parameters of the tumor, the longitudinal tumor length and the length of the muscle layer interruption (MLI) were measured. Longitudinal tumor length was defined as the distance from the oral edge to the anal edge of the cancerous tissue. When the cancer specimen was divided into several sections, each diameter was added. The length of the MLI was defined as the length from the oral edge to the anal edge of the outer muscle layer ruptured by tumor invasion.

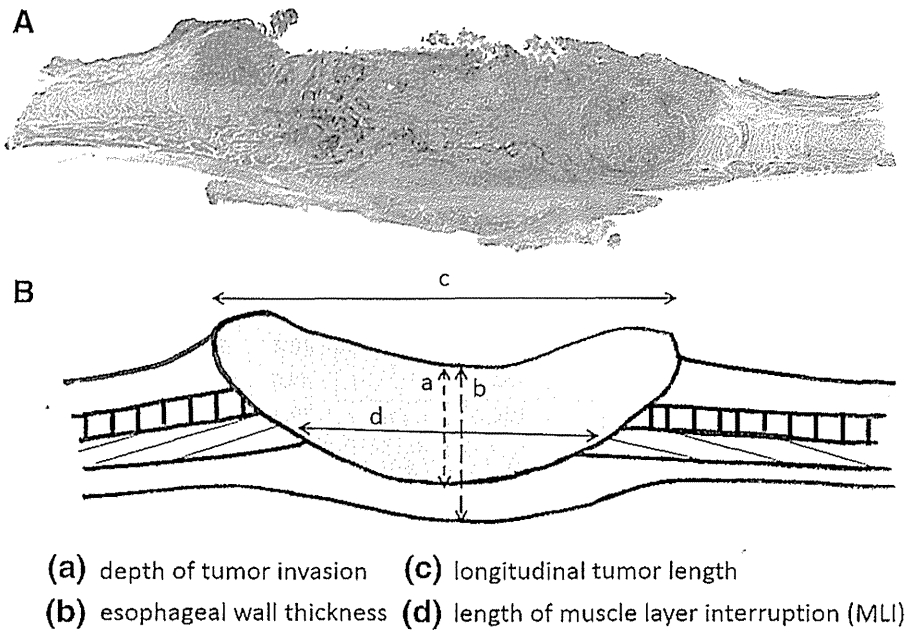


Fig. 1 Method of measuring the four pathological parameters (**a**, **b**). As the vertical parameters of the tumor, the depth of tumor invasion (a) and esophageal wall thickness (b) were measured. As the horizontal parameters of the tumor, the longitudinal tumor length (c) and length of the ruptured outer muscle layer (d) were measured

Statistical analysis

Continuous variables are expressed as the mean ± SD. A χ^2 test or Fisher's exact test was used to compare categorized variables. The Wilcoxon test was used to compare continuous variables. Overall survival was calculated from the date of the operation to the occurrence of the event or to the last known date of follow-up. Actual survival was calculated with the Kaplan–Meyer method and statistically evaluated by the log-rank test. The Cox proportional hazards regression model was used to analyze the simultaneous influence of prognostic factors. All calculations were performed using JMP ver. 8.0.1 software, and a p value of <0.05 was considered significant.

Results

Patient characteristics

The clinico-pathological characteristics of the patients and tumor specimens are shown in Table 1. The median age of the patients was 64.5 (range 30–85) years. In histological type, 263 (98.1 %) were squamous cell carcinomas and 5 (1.9 %) were basaloid carcinomas. Tumor locations were the upper third (10.4 %), middle third (49.6 %), and lower third (39.9 %) of the esophagus. Organs invaded in 30 cases with T4 tumors were as follows: 3 cases of invasion to the aorta, 6 cases of invasion to the bronchial tree, 4 cases of invasion to the pericardium, 12 cases of invasion to the diaphragm, 3 cases of invasion to the lung, one case of invasion to the thoracic duct, and one case of invasion to the thyroid. 255 patients (95.1 %) were curatively resected while 13 patients were not; 3 patients were R1 resection and 10 were R2 resection. The 13 patients who were R1/R2 resection consisted of 2 pT3 patients and 11 pT4 patients.

The association between T factor and the four measured morphological parameters

The results of measurements of the four morphological parameters are shown in Fig. 2. In vertical measurements, the mean depth of tumor invasion was 2.7 mm in T1, 5.9 mm in T2, 8.6 mm in T3, and 11.9 mm in T4. The mean esophageal wall thickness was 4.9 mm in T1, 7.4 mm in T2, 9.6 mm in T3, and 13.7 mm in T4. These results showed that there was a significant correlation between these two vertical parameters and T stage ($p < 0.0001$ and $p < 0.0001$, respectively). In the horizontal measurement, the mean longitudinal tumor length was 17.6 mm in T1, 28.8 mm in T2, 43.2 mm in T3, and 56.8 mm in T4. The mean length of MLI was 21.3 mm in T3 and 39.4 mm in T4. There was also a significant correlation between these two horizontal parameters and T factor ($p < 0.0001$ and $p < 0.0001$, respectively).

Subclassification of T3 tumors

Next, we examined whether we could divide T3 tumors into two groups according to patient prognosis using the four morphological parameters. We attempted to identify the most clinically relevant cutoff value of the four pathological parameters by focusing on hazard ratios. As a result, a 7.5-mm depth of tumor invasion, 7.5-mm

Table 1 Characteristics of 268 esophageal cancer patients

Characteristics of patients	Number	%
Age (years)		
Median	64	
Range	30–85	
Sex		
Males	241	89.9
Females	27	10.1
Location		
Upper	28	10.4
Middle	133	49.6
Lower	107	39.9
pT		
pT1	103	38.4
pT2	32	11.9
pT3	103	38.4
pT4	30	11.2
pN		
pN0	100	37.3
pN1	79	29.5
pN2	60	22.4
pN3	29	10.8
cM		
cM0	239	89.1
cM1 (lym)	29	10.8
Lymphatic invasion		
ly0	67	25.0
ly1–3	201	75.0
Venous invasion		
v0	158	59.0
v1–2	110	41.0
Lymph node dissection		
2-field	170	63.4
3-field	98	36.6
Curability		
R0	255	95.1
R1	3	1.1
R2	10	3.7

esophageal wall thickness, 40-mm longitudinal tumor length, and 20-mm length of MLI were identified as optimal cutoff values. Using these four values, we were able to divide T3 tumors into two groups according to patient prognosis (Fig. 3). Among the four morphological parameters, the length of MLI was the most reliable parameter for predicting the prognosis of patients with T3 tumors. The 3- and 5-year survival rate was 63.4 and 59.5 %, respectively, in patients with <20 mm MLI, and 36.7 and 26.7 % in patients with ≥20 mm MLI ($p = 0.009$, hazard ratio 2.41). Patients with T3 tumors that were <20 mm MLI had a survival similar to those with T2 tumors. In contrast, patients with T3 tumors with ≥20 mm MLI had a poor prognosis that was similar to those with T4 tumors (Fig. 4). There was no significant association between the length of MLI and the clinico-pathological findings like lymph node involvement, tumor location, and venous/lymphatic invasion.

Multivariate prognostic analyses using clinical parameters including age, sex, tumor location, number of lymph node metastases, distant metastasis, depth of tumor invasion, esophageal wall thickness, longitudinal tumor length, and length of MLI showed that the number of lymph node metastases and the length of MLI were independent prognostic factors in patients with T3 esophageal cancer (Table 2).

Pattern of recurrence in T3 tumors

Of 103 patients with T3 tumors, recurrence was observed in 58 patients (56.3 %). Whereas the rate of recurrence was 46.9 % in patients with tumors that had <20 mm MLI, 64.3 % of those with ≥20 mm MLI had recurrences. This difference did not reach statistical significance ($p = 0.110$, Table 3). There was no significant difference between the two groups with regard to hematogenous recurrence and lymph node recurrence. However, local recurrence was more frequent in patients with tumors with ≥20 mm MLI than in those with tumors with <20 mm MLI (4.3 vs. 21.4 %, $p = 0.019$).Among local recurrences, both connective tissue recurrence (Fig. 5a) and pleural dissemination (Fig. 5b) were less frequent in those with <20 mm MLI than in those with ≥20 mm [0 patient (0 %) vs. 6 patients (10.7 %) and 2 patients (4.3 %) vs. 8 patients (14.3 %), respectively].

Discussion

T3 esophageal cancer accounts for the majority of esophageal cancers. In the present study, we evaluated whether T3 esophageal cancers can be subclassified into subgroups using morphological parameters. The results showed that the length of MLI was the most significant morphological parameter that possibly indicates the prognosis of patients with T3 esophageal cancer. Moreover, the length of MLI was identified as an independent prognostic factor in patients with T3 esophageal cancer.

There have been several previous studies that showed that tumor length is associated with prognosis inpatients with esophageal cancer. Wang et al. [13] examined the longitudinal tumor length of 582 esophageal squamous cell carcinoma patients who underwent surgical resection as the primary treatment. Their results demonstrated that patients

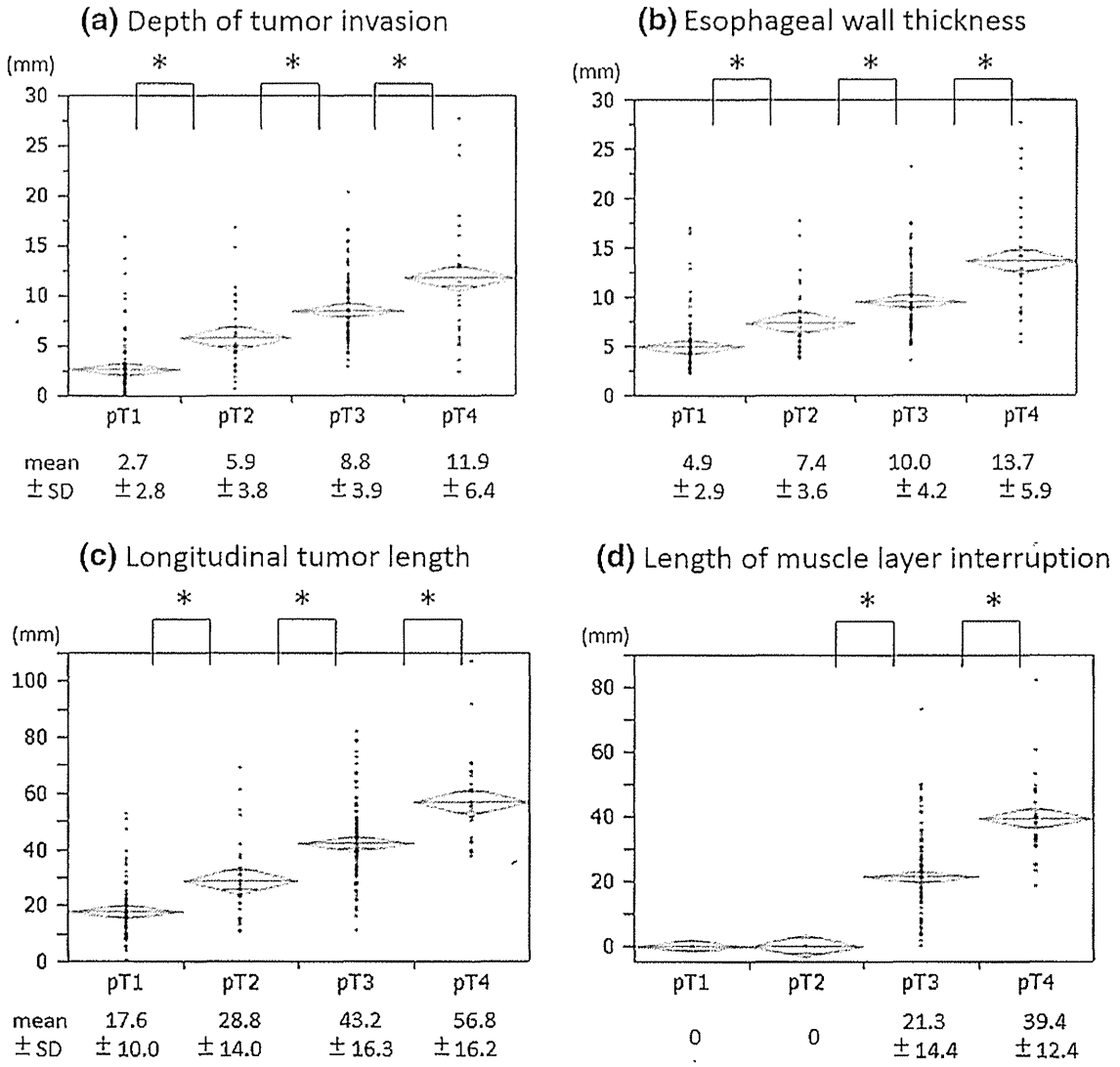


Fig. 2 The association between T stage and the results of the four morphological parameter measurements. There was a significant correlation between these four morphological parameters and T stage ($p < 0.0001$ and $p < 0.0001$, respectively). Data are shown as the mean ± standard deviation (SD). *$p < 0.05$

with tumors 3 cm or less in length had longer survival than patients with tumors with lengths longer than 3 cm, and that tumor length was an independent prognostic factor in multivariate analysis. Griffiths et al. [14] also investigated the tumor lengths of 309 esophageal cancer patients who underwent esophageal resection. Their study showed that tumor lengths greater than 35 mm were associated with worse overall survival compared with shorter tumors. They also concluded that tumor length remained a significant prognostic factor in multivariate analysis. In our study, longitudinal tumor length was associated with T stage and patients with T3 tumors that were longer than 40 mm had shorter survival compared with patients with tumor lengths of 40 mm or less. However, the length of the ruptured outer muscle layer was a better indicator of survival than longitudinal tumor length in patients with T3 esophageal cancer. To our knowledge, this is the first report showing that length of MLI is related to patient prognosis.

In clinical practice, T stage is usually determined by an axial image from computed tomography and/or magnetic resonance imaging. Our results indicate that an evaluation of the longitudinal image should help in the preoperative diagnosis of advanced esophageal cancers.

In this study, patients whose T3 tumor had ≥20 mm MLI had a worse prognosis than those with tumors with <20 mm MLI. The prognosis of patients with T3 tumors with ≥20 mm MLI was similar to the prognosis of patients with T4 tumors. The reason for this result may be that patients whose T3 tumor has ≥20 mm MLI have a higher frequency of local recurrence including connective tissue

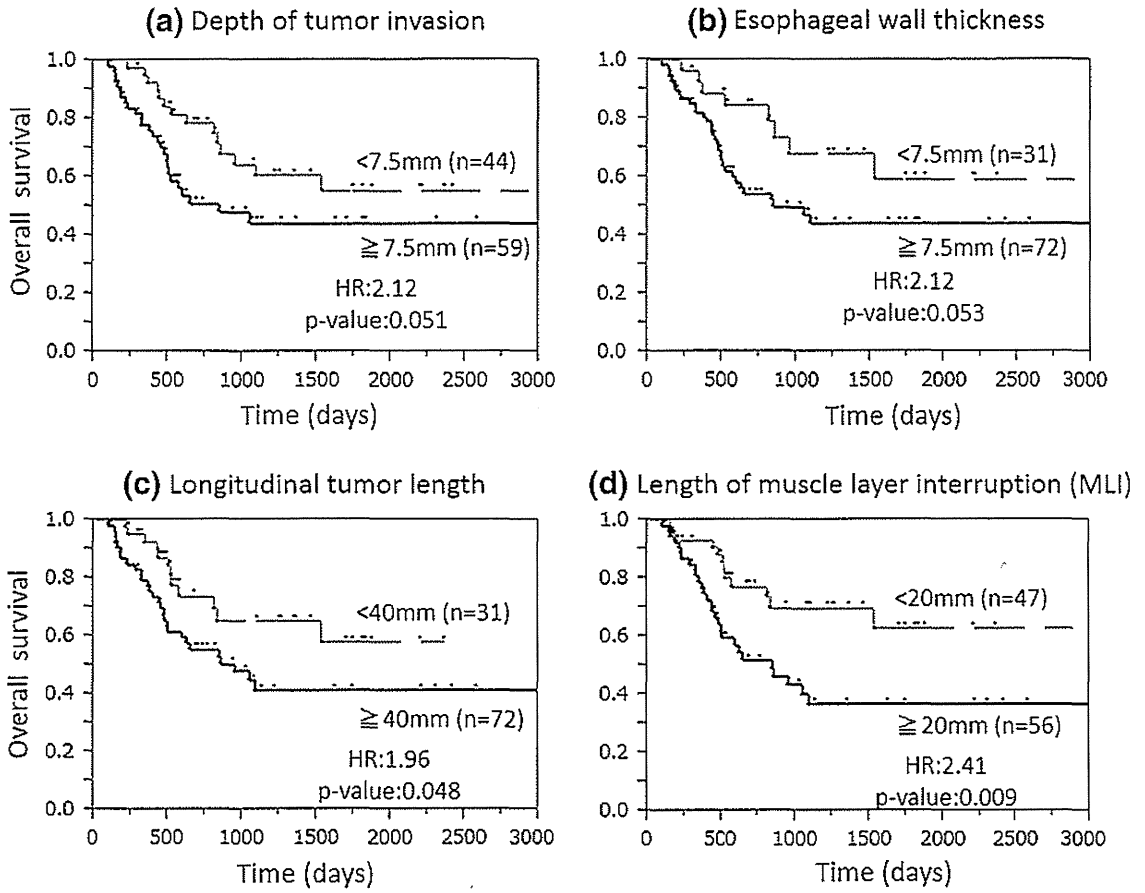
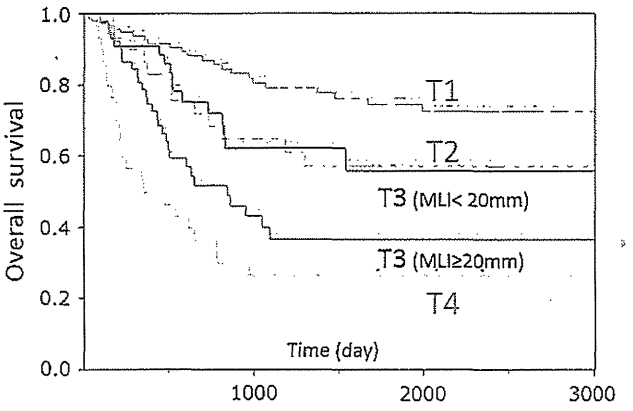


Fig. 3 Kaplan–Meier overall survival curves based on the four morphological parameters. Patients were divided into groups based on the optimal cutoff values; 7.5 mm in depth of tumor invasion, 7.5 mm in esophageal wall thickness, 40 mm in longitudinal tumor length, and 20 mm in length of muscle layer interruption (MLI). Among the four parameters, length of MLI was most reliable in predicting the prognosis of T3 esophageal patients

recurrence and dissemination. This means that there is possibility of some tumor cells remaining even after a complete tumor resection in those with T3 tumors with ≥20 mm MLI. In other words, T3 tumors with ≥20 mm MLI may be microscopic T4 tumors in terms of micro invasiveness. Pathological examinations showed that esophageal cancers frequently exhibit tumor cells scattered in the boundary of the surrounding tissue, such as "tumor budding". Miyata et al. [15] reported that high-grade tumor budding was observed in 40.8 % of esophageal cancer patients and that these patients had lower survival than those in the low-grade group. Taken together, T3 tumors with ≥20 mm MLI should be regarded as potential T4 tumors.

We regarded both pleural dissemination and connective tissue recurrence as local recurrences. In esophageal cancer patients, we reported previously that positive lavage cytology was rarely observed at the thoracotomy [16–19], but was frequent at the end of the esophagectomy. In addition, positive lavage cytology was associated with advanced tumor invasion, pleural dissemination recurrence,



	3-year survival	5-year survival
T1	79.4	74.8
T2	65.0	59.5
T3 (MLI<20mm)	63.4	59.1
T3 (MLI≥20mm)	36.7	36.7
T4	26.7	26.7

Fig. 4 Kaplan–Meier overall survival curves by T stage and length of muscle layer interruption (MLI). Patients with T3 tumors with <20 mm MLI had survivals similar to those with T2 tumors. In contrast, patients with T3 tumors with ≥20 mm MLI had a poor prognosis similar to those with T4 tumors

Table 2 Multivariate survival analyses of 103 patients with T3 esophageal cancer

	Hazard ratio	95 % CI	*p* value
Age (<65/≥65)	1.05	0.49–1.87	0.891
Sex (M/F)	2.82	0.76–18.4	0.131
Location (Ut Mt/Lt)	1.89	0.95–3.63	0.071
Number of pN (<3/≥3)	2.82	1.34–5.96	0.007
M0/M1	1.91	0.18–1.38	0.196
Depth of tumor invasion (<7.5/≥7.5 mm)	1.50	0.63–4.16	0.381
Esophageal wall thickness (<7.5/≥7.5 mm)	1.21	0.37–3.77	0.744
Longitudinal tumor length (<40/≥40 mm)	1.02	0.44–2.43	0.969
Length of MLI (<20/≥20 mm)	3.18	0.35–7.87	0.008

CI confidence interval, *Ut* upper, *Mt* middle, *Lt* lower, *MLI* muscle layer interruption

Table 3 Difference of recurrence pattern by the length of muscle layer interruption

Recurrence pattern	MLI <20 mm ($n = 47$)	MLI ≥20 mm ($n = 56$)	*p* value
Hematogenous	11 (23.4)	10 (17.9)	0.624
Liver	4 (8.5)	4 (7.1)	–
Lung	5 (10.6)	4 (7.1)	–
Bone	4 (8.5)	4 (7.1)	–
others	1 (2.1)	1 (1.8)	–
Lymph node	19 (40.4)	21 (37.5)	0.840
Local	2 (4.3)	12 (21.4)	0.019
Recurrence total	22 (46.9)	36 (64.3)	0.110

MLI muscle layer interruption

and poor prognosis [19]. This result suggests that pleural dissemination after esophagectomy is associated with local spread of the primary tumor and microscopic residual cells after surgery.

Postoperative radiotherapy may help prevent connective tissue recurrence in patients with ≥20 mm MLI, but may not be effective for patients with <20 mm MLI. Moreover, we expected that preoperative chemo- or radiotherapy might be able to reduce local recurrences including both pleural dissemination and connective tissue recurrence. Several clinical trials showed an obvious survival benefit of preoperative chemo- and chemoradiotherapy for advanced esophageal cancers [20–31]. We found that patients with a good response to preoperative chemotherapy had less tumor budding [15]. Preoperative evaluation of MLI should be done before prescribing neoadjuvant therapies. To use the current results for the choice of preoperative treatment for T3 esophageal cancer, translating pathological parameters such as length of MLI into imaging techniques used clinically such as endoscopic ultrasonography [32, 33], magnetic resonance imaging [34, 35], and fluorodeoxyglucose positron emission tomography [36, 37] will be required.

In this study, we examined only the cases in which none of therapy is performed prior to surgery, because we think that neoadjuvant therapy can make it difficult to examine the significance of MLI due to therapeutic modification.

However, recently, most of patients with advanced esophageal cancer undergo preoperative therapy such as neoadjuvant chemotherapy or chemoradiotherapy. Therefore, we will examine the prognostic significance of MLI in patients who undergo neoadjuvant therapy followed by surgery in next study.

In summary, we demonstrated that evaluating the length of MLI is potentially useful for predicting survival in patients with T3 esophageal cancer. Moreover, patients

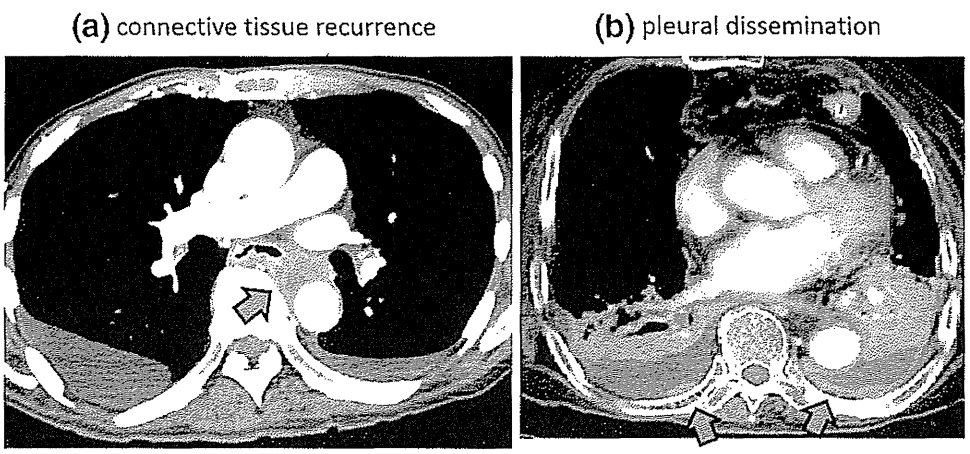


Fig. 5 Computed tomography of local recurrences of esophageal carcinoma. **a** *Arrow* shows connective tissue recurrence. **b** *Arrows* show thickened pleura, which exhibits pleural dissemination

with T3 tumors with ≥20 mm MLI had a higher frequency of local recurrences and disseminated recurrences. To apply the current results in the clinical setting, further studies will be needed.

Ethical Statement Our studies are performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and subsequent revisions. Written informed consent was obtained from participants.

Conflict of interest The authors declare no support.

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DYNAMIC MANUSCRIPTS

Automatic smoke evacuation in laparoscopic surgery: a simplified method for objective evaluation

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Abstract
Background Although its theoretical usefulness has been reported, the true value of automatic smoke evacuation system in laparoscopic surgery remains unknown. This is mainly due to the lack of objective evaluation. The purpose of this study was to determine the efficacy of the automatic smoke evacuator in laparoscopic surgery, by real-time objective evaluation system using an industrial smoke-detection device.
Methods Six pigs were used in this study. Three surgical ports were placed and electrosurgical smoke was generated in a standard fashion, using either a high-frequency electrosurgical unit (HF-ESU) or laparosonic coagulating shears (LCS). The smoke was evacuated immediately in the evacuation group but not in the control nonevacuation group. The laparoscopic field-of-view was subjectively evaluated by ten independent surgeons. The composition of the surgical smoke was analyzed by mass spectrometry. The residual smoke in the abdominal cavity was aspirated manually into a smoke tester, and stains on a filter paper were image captured, digitized, and semiquantified.
Results Subjective evaluation indicated superior field-of-view in the evacuation group, compared with the control, at 15 s after activation of the HF-ESU ($P < 0.05$). The smoke comprised various chemical compounds, including known carcinogens. The estimated volume of intra-abdominal residual smoke after activation of HF-ESU was significantly lower in the evacuation group (47.4 ± 16.6) than the control (76.7 ± 2.4, $P = 0.0018$). Only marginal amount of surgical smoke was detected in both groups after LCS when the tissue pad was free from burnt tissue deposits. However, the amount was significantly lower in the evacuation group (21.3 ± 10.7) than the control (75 ± 39.9, $P = 0.044$) when the tissue pad contained tissue sludge.
Conclusions Automatic smoke evacuation provides better field-of-view and reduces the risk of exposure to harmful compounds.

Keywords Automatic smoke evacuator · Laparoscopic surgery · High-frequency electrosurgical unit · Laparosonic coagulating shears · Smoke tester

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The smoke generated during electrosurgery reduces visibility in laparoscopic surgery and is harmful not only for the patients but also for surgeons and operating room personnel [1]. In fact, some groups have advocated removal of the surgical smoke using a closed circuit, based on their findings of the presence of various potentially harmful substances in the surgical smoke [2, 3]. In daily practice, however, many laparoscopists release the surgical smoke from the abdominal cavity into the room air, by opening the stopcock of the laparoscopic port [3]. Although

commercially available, an automatic smoke evacuation system has not been used widely, mainly because of lack of objective evaluation. The purpose of this study was to evaluate the efficacy of a commercially available automatic smoke evacuator in eliminating surgical smoke, including harmful substances, in experimental laparoscopic surgery, using an industrial smoke-testing device.

Materials and methods

The experimental protocol described in this study was reviewed and approved by the Animal Care and Ethical Review Committee of Osaka University. All animals used in the experiments were sacrificed at the end of the study by deep anesthesia.

Three month-old female, 35-kg domestic swine (LWD swine, $n = 6$) were fasted overnight before the experiment. Premedication with intramuscular ketamine 10 mg/kg and xylazine 2 mg/kg were administered. After settling in supine position, the animal was intubated and a catheter was cannulated into an ear vein to maintain general anesthesia using 1–3 % isoflurane inhalation. The first trocar for optics was placed midabdomen using open Hasson method, while each of the other two working ports was placed in the lateral abdomen. Carbon dioxide (CO_2) pneumoperitoneum was established using a standard automatic CO_2 insufflator (UHI-3; Olympus Medical Systems, Tokyo, Japan) with an intra-abdominal pressure of 8 mmHg. Air-tightness was secured by adding a lubricant around each port site. The abdominal cavity was then explored with a rigid-tip, high-definition videolaparoscope (OTV-S7 ProH-HD-12E, Olympus Medical Systems, Tokyo) before the surgical procedures.

The liver surface was exposed laparoscopically and burnt for 30 s to generate smoke in a reproducible fashion, using a laparoscopic hook-shaped electrosurgical probe connected to a high-frequency electrosurgical unit (HF-ESU, VIO300D; ERBE Elektromedizin, Tübingen, Germany) or a laparosonic coagulation shares (LCS, Harmonic®; Ethicon Endo-Surgery, Cincinnati, OH). In the evacuation group, an automatic smoke evacuator (IES2; ERBE), at maximum power (100 %) and delay time of 10 s, equipped with a smoke absorptive membrane (#7-510-16; Northgate Technologies Inc, Scottsdale Court, IL), was connected to one of the working ports via a standard insufflation tube (Fig. 1A). The smoke was simultaneously evacuated while the energy device was activated with the delay time. The absorptive membrane was replaced every two times during the experiment to maintain the maximal absorptive performance of the evacuation system. In the nonevacuation control group, the experiment was repeated without the use of the evacuator (Fig. 1B).

Subjective evaluation of laparoscopic field of view by laparoscopists

Video images of the surgical field were recorded in each group (Movie 1) every 5 s (0–40 s: total 9 images in each group). Each recording was evaluated by ten well-trained surgeons into four grades (excellent, good, fair, and poor surgical view) using appointed questionnaire (Fig. 2A).

Sampling of residual smoke after activation of energy devices

After the activation of energy devices, a smoke tester (Bacharach Smoke Tester, HT-1650; Hodaka, Osaka, Japan) with a dedicated filter paper (HT-1651; Hodaka) was

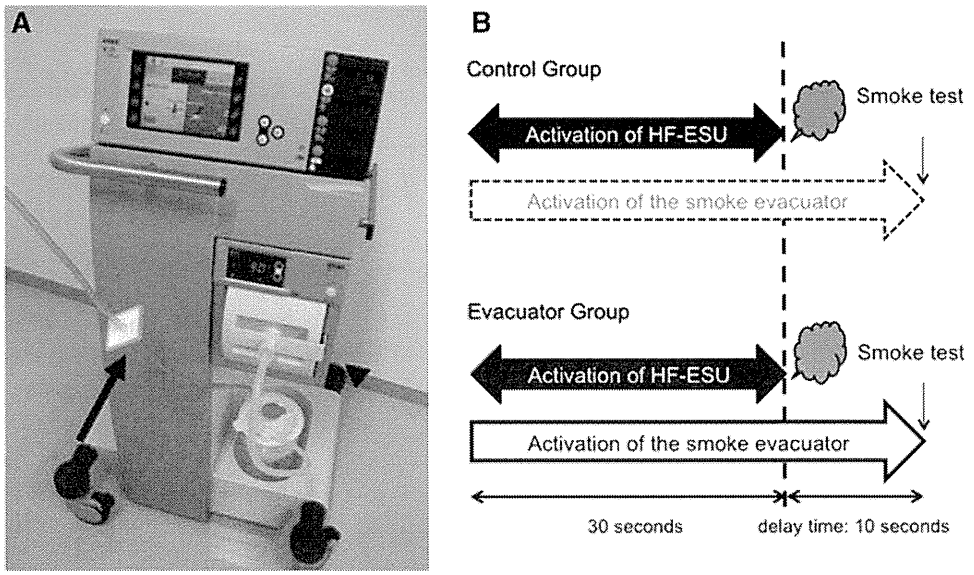
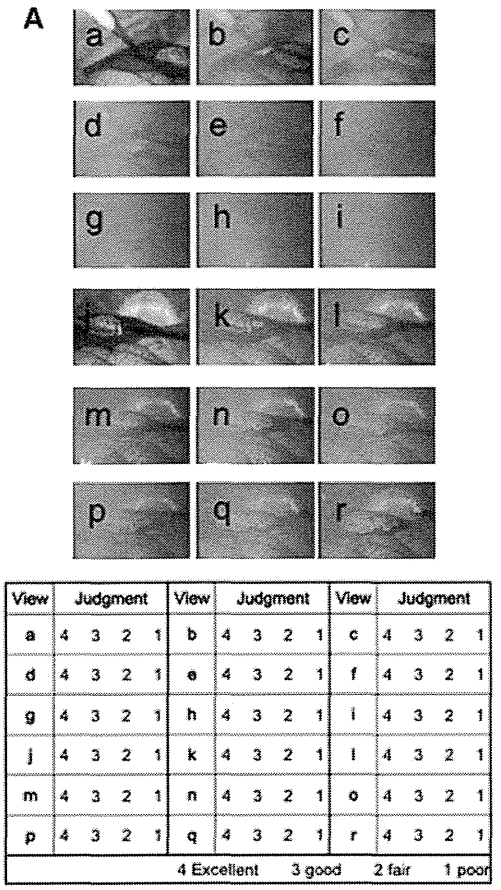


Fig. 1 **A** VIO300D connected with IES2 (*arrowhead*). IES2 evacuates smoke from the abdominal space by using a membrane filter (*arrow*). **B** The experimental protocol in the evacuator and control groups



View	Judgment	View	Judgment	View	Judgment
a	4 3 2 1	b	4 3 2 1	c	4 3 2 1
d	4 3 2 1	e	4 3 2 1	f	4 3 2 1
g	4 3 2 1	h	4 3 2 1	i	4 3 2 1
j	4 3 2 1	k	4 3 2 1	l	4 3 2 1
m	4 3 2 1	n	4 3 2 1	o	4 3 2 1
p	4 3 2 1	q	4 3 2 1	r	4 3 2 1

4 Excellent 3 good 2 fair 1 poor

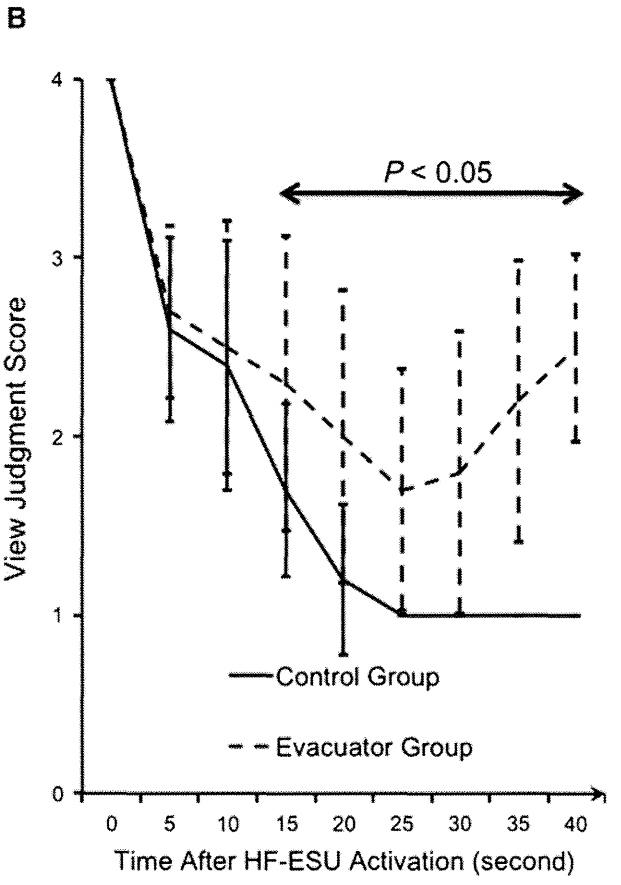


Fig. 2 **A** Image-captured laparoscopic fields of views and appointed questionnaire for subjective evaluation (*bottom*). **B** Results of subjective evaluation of the fields of views by surgeons. The evacuator group outperformed the control group from 15 to 40 s after activation of the HF-ESU ($P < 0.05$)

subsequently connected to the working port (Fig. 3A), and the residual smoke in the abdominal cavity was manually aspirated ten times according to the protocol provided by the manufacturer (Movie 2). Stained filter papers (Fig. 3B) were used in the following procedures.

Component analysis of sampled surgical smoke and membrane

The stained filter paper of each group, the membrane in the closed circuit after use (Fig. 3C, left: before use, right: after use) as a positive control and unstained filter paper as a negative control were cut into small pieces and placed into head space vials, respectively. Vaporization of each sample was performed using TurboMatrix HS40 (Simadzu, Kyoto, Japan) under the following conditions; injection duration: 0.25 min, heat treatment temperature: 120 °C, needle temperature: 120 °C, compression duration: 1 min, incubating duration: 30 min and pressure: 120 kPa. Gas chromatography and mass spectrum (GC–MS) analysis were performed using QP2010 Ultra (Simadzu).

Conversion to carbon concentration of stained filter papers

The stain on the filter paper was digitized (Fig. 4A, top column) using an image scanning device (CanoScan 8800F; Canon, Tokyo). Each image was then converted to a grayscale (Fig. 4A, middle column) using an image retouching software (Photoshop ver. 7; Adobe Systems, San Jose, CA), and semiquantified (Fig. 4A, lower column) using an image analysis software (NIH image ver. 1.63, National Institutes of Health, Washington, D.C.). Conversion to carbon concentration was performed by using a standard scale (RR776, Bacharach, Fig. 4B).

Real-time objective evaluation of residual smoke after activation of energy devices

HF-ESU challenge

The liver surface was exposed laparoscopically and burnt for 30 s with the HF-ESU. The setting of HF-ESU was splay coagulation mode (Effect: 2 100 W) and 30 s (VIO Time Limit; 30 s). The experiment was repeated twice in

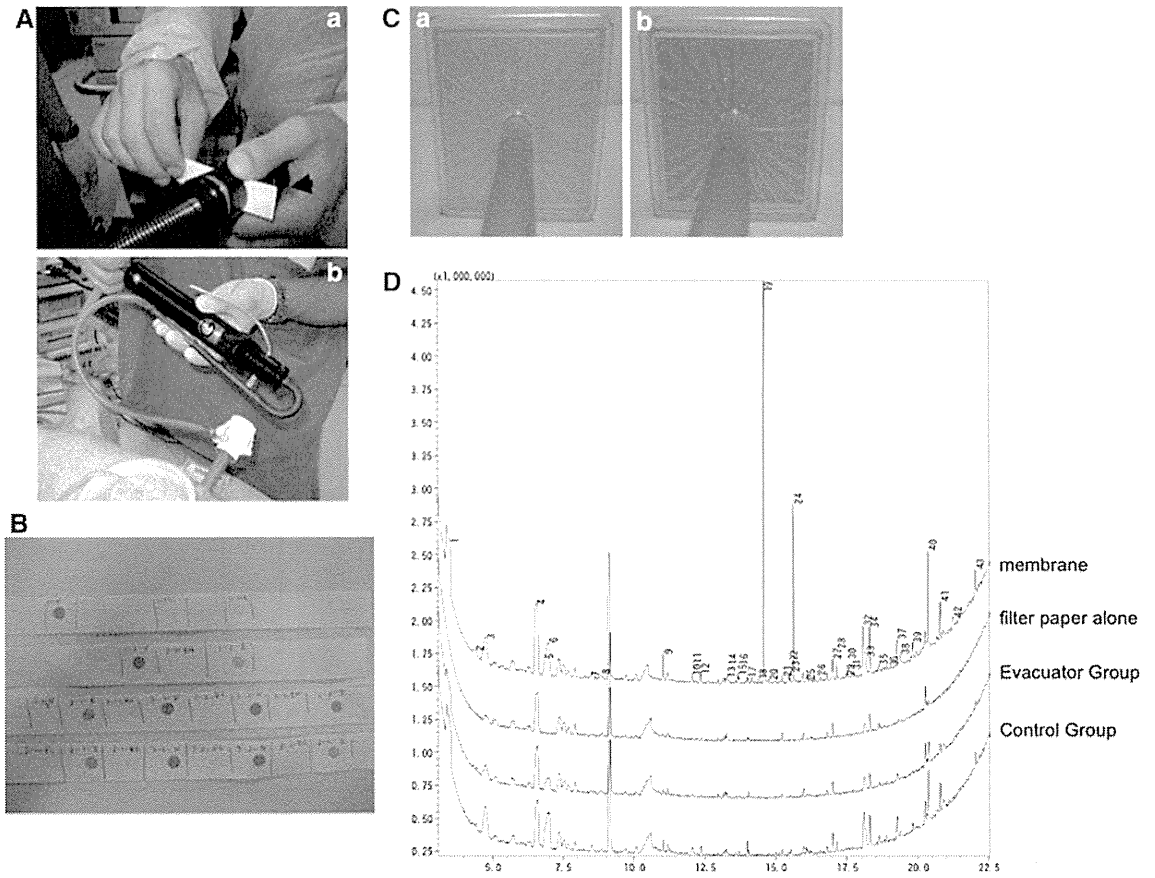


Fig. 3 The industrial smoke tester. (*a*) Filter paper (*arrow*) was fitted to the cylinder of the smoke tester. (*b*) The smoke tester equipped with filter paper was connected to the working port. **A** Collected surgical smoke on the filter papers. **B** Smoke absorptive membranes used in the smoke evacuation system: (*a*) before use, (*b*) after use. **C** Results of GC–MS analysis (membrane: smoke absorptive membrane). **D** Peak values are shown at the *top* of each peak

each animal of each group, i.e., six times overall in the crossover turn.

LCS challenge

A similar experiment was conducted using LCS instead of the HF-ESU. LCS was applied to the liver edge for 30 s to generate a "mist," with or without automatic evacuation. The LCS was set at level 5. This protocol was adopted because in daily practice, surgeons frequently encounter further deterioration of laparoscopic vision with the mist, especially when the tissue pad of LCS is covered with sludge. The experiment was accordingly conducted under two different conditions: a clean pad, and a dirty pad with the burnt deposits (Fig. 5B). Because the currently used IES2 is not compatible with the LCS system, the mist was evacuated by activating IES2 with a foot pedal while LCS was activated. The experiment was repeated twice in each animal of each group, i.e., six times overall in the crossover turn. Data of the two groups were compared.

Statistical analysis

Statistical analyses were performed using JMP 8.0.1 for Windows (SAS Institute, Cary, NC). Possible differences between the two groups in each experiment were analyzed using the Student's t test, χ^2 test, or Wilcoxon test as appropriate. A probability level of 0.05 was selected to indicate the statistical significance.

Results

Subjective evaluation of the surgical smoke generated by a HF-ESU

Assembling questionnaires described by ten surgeons revealed that the fields of laparoscopic views in the evacuator group were better than those of the control group at 15–40 s after activation of HF-ESU ($P < 0.05$; Fig. 2B).

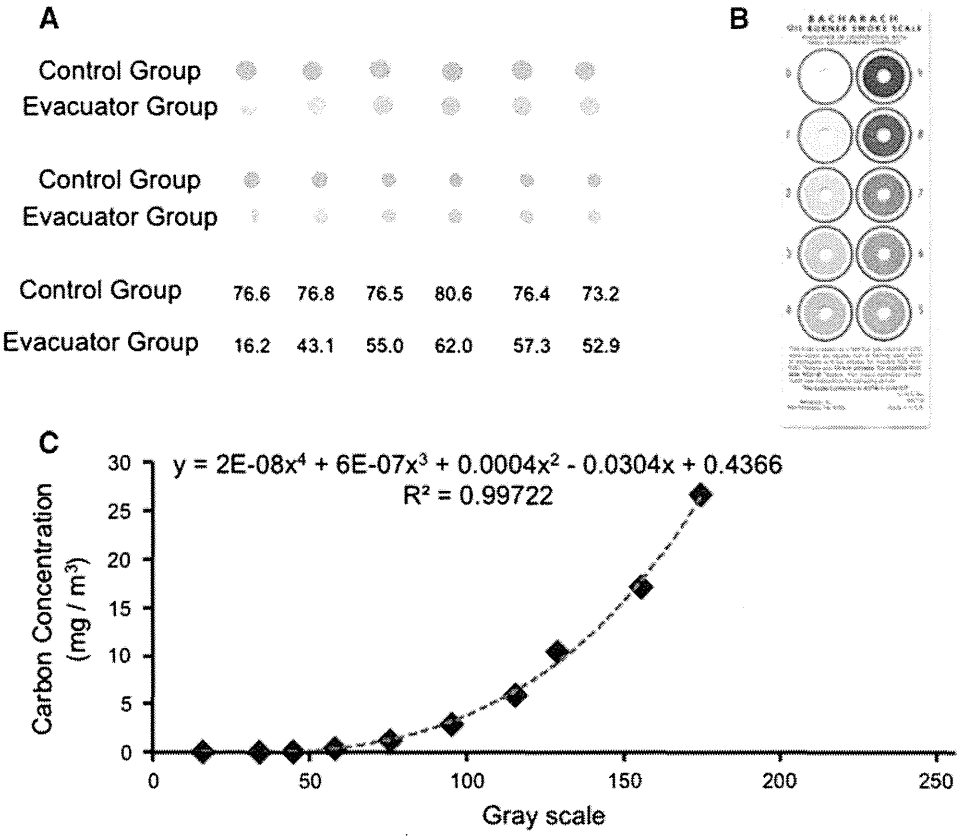


Fig. 4 **A** Semiquantification of surgical smokes collected on the filter papers. Filter papers were image scanned through a common scanning device (*top*). The scanned stains were converted to a gray scale (*middle*), and then, semiquantified through Image J software (*bottom*). **B** Standard smoke scale supplied with the testing system. **C** The formula used for conversion of the scored stains to carbon concentration

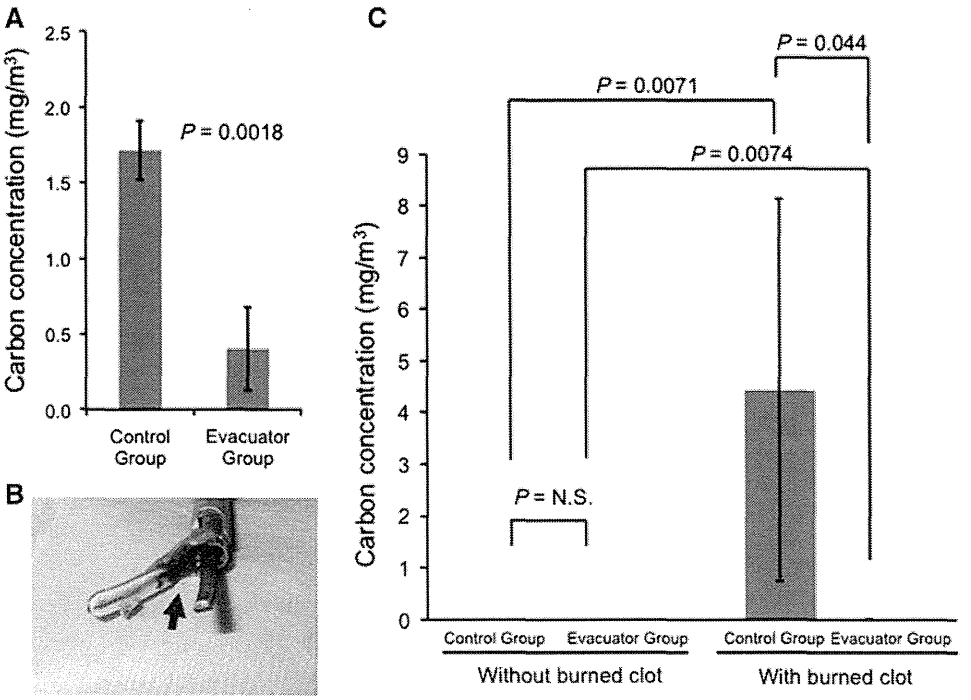


Fig. 5 **A** Semiquantification of carbon concentration in the smoke after HFS-ESU activation. The carbon concentration was significantly lower in the evacuator group than the control ($P = 0.0018$). **B** LCS with sludge in the tissue pad. **C** Semiquantification of carbon concentration after LCS activations under two different conditions. Without burned clot: only a few carbon compounds were detected in both groups; with burned clot: carbon concentration increased in both groups (control: $P = 0.0071$, evacuator: $P = 0.0074$). This tendency was intensified in the control group than in evacuator group ($P = 0.044$)

Analysis of component included in surgical smoke

The GC–MS analysis identified 42 peaks in the positive control (Fig. 3D) and 37 substances (Table 1). The detected substances were carbon compounds and three were carcinogenic according to the International Agency for Research on Cancer (IRAC) (acetaldehyde: group I; dimethylformamide: group 2B; and furfural: group 3). As

Table 1 Chemical compounds detected in this study

Peak number	Substance name	LTEL	STEL	Toxic or harmful effects IRAC Group
1	Acetaldehyde	37	92	Group 1
2	Propanol	500	625	
3	Acetone	1,210	3,620	
4	Methyl alcohol	266	333	
5	2-Methylbutanol			
6	3-Methylbutanol			
7	2,3-Butanedione			
8	Pentanol			
9	Hexanal			
10	Isopropenyl methyl ketone			
11	1-Methoxy-2-propanol	375	560	
12	*n*-Butanol	–	154	
13	Heptanal			
14	Dodecane			
15	–			
16	–			
17	Ethylene glycol ethyl ether			
18	2-Pentylfuran			
19	3,3,4,4,5,5,6,6,7,7,8,8-Tridecafluoro-1-octanol			
20	–			
21	Octanol			
22	1-Hepten-3-one	166	475	
23	1-Hydroxy-2-propanone			
24	3,3,4,4,5,5,6,6,7,7,8,8-Tridecafluoro-1-octanol			
25	–			
26	Dimethylformamide	30	61	Group 2B
27	Nonanal			
28	Ethylene glycol butyl ether			
29	*N*,*N*-Dimethylacetamide	36	72	
30	1,3-Ditertiarybutylbenzene			
31	1-Octen-3-ol			
32	Acetic acid			
33	Furfural	8	20	Group 3
34	2-Ethylhexanol			
35	Decanal			
36	Pyrrole			
37	Benzaldehyde			
38	Propanoic acid	31	46	
39	Ethylene glycol isopropyl ether	50.1		
40	Diethylene glycol ethyl ether	101		
41	2-Furanmethanol			
42	3-Methylbutanoic acid			
43	–			

LTEL and STEL are described in the EH40/2005 workplace exposure limits (available at http://www.hse.gov.uk/pubns/books/eh40.htm). International Agency for Research on Cancer (IRAC) monographs on evaluation of carcinogen risks to humans (available at http://monographs.iarc.fr/)

LTEL long-term exposure limit (8-h TWA reference period) mg/m^{-3}, *STEL* short-term exposure limit (15-min reference period) mg/m^{-3}, – not specified

shown in Fig. 3D, all peaks on the total ion chromatogram (TIC) of the positive control fitted closely with those of the stained filter paper samples in each group.

Validation of real-time carbon concentration monitoring

To rationalize the scanning devices and NIH software used in this study, we scanned a standard smoke scale pertaining to the testing system (RR776, Bacharach, Inc., New Kensington, PA; Fig. 4B), and converted the obtained images to grayscale images for semiquantification. The scores of the smoke scale correlated linearly and significantly with the grayscale concentration in function ($R^2 = 0.992$, data not shown). These results confirmed the appropriateness of the current experimental setting. Next, standard smoke scales were beforehand appointed carbon concentrations. We used these standard concentrations to convert the grade of stains on the filter papers to carbon concentrations as follows:

$$y = 2\mathrm{E} - 08x^4 + 6\mathrm{E} - 07x^3 + 0.0004x^2 - 0.0304x + 0.4366,$$

where y is the carbon concentration (mg/m^3), and x is the stains converted to standard scores ($R^2 = 0.9972$).

Real-time objective evaluation of residual smoke after activation of energy devices

HF-ESU challenge

As shown in Fig. 5A, the semiquantified carbon concentration was significantly lower in the evacuator group (0.4 ± 0.27 mg/m^3) than the control group (1.7 ± 0.02 mg/m^3, $P = 0.0018$).

LCS challenge

When using LCS with a clean pad, test stains were only marginally detectable and there was no significant difference in the smoke concentration between the two groups (Fig. 5C; evacuator group: 0.002 ± 0.0078 control group: 0.0023 ± 0.0085 mg/m^3, $P = 0.96$). On the other hand, the use of LCS with a sludge in the crotch of the tissue pad significantly lowered the residual smoke concentration (Fig. 5C; evacuator group: 0.018 ± 0.01, control group: 4.4 ± 3.7 mg/m^3, $P = 0.044$).

Discussion

The smoke generated during electrosurgery causes not only surgeon's stress and prolongation of operating time [4] but also places both patients and operating room personnel at risk of exposure to harmful substances [1, 5–10]. High temperature decomposition generated during tissue ablation is known to produce breathable aerosols, complex organic chemicals, and cellular debris, including carcinogenic substances [4]. The composition of the surgical smoke includes various chemicals, such as aldehydes, benzene, toluene, acrolein, hydrocyanic gases, and carbon monoxide [6, 8, 11–13]. Therefore, the smoke generated by tissue decomposition is presumably cytotoxic, genotoxic, mutagenic, and clastogenic for all operating room crew [6, 8, 11–13]. Accordingly, the use of automatic smoke evacuation systems that work simultaneously with the energy device seems logical. Such devices, however, are not commonly used in daily practice, mainly because of the need for another device setup, additional cost, and particularly lack of objective validation.

In this study, we used IES2 as a representative commercially available smoke evacuator. The 30-s activation of energy devices was adopted, because the visualization obtained after the 30-s activation was very similar to that in daily practice, when we surgeons rebuffed our effort to arrest hemorrhage. Although smoke was generated in the experimental setting, the field of view in the evacuator group was better than that of the control group in subjective evaluation by ten independent well-trained surgeons. Next, we sampled the surgical smoke under various conditions for quantitative analysis. The smoke tester is an authorized device for the assessment of workplace environment by semiquantifying floating carbon compounds in the air. The industrial method was used based on the reported presence of carbon compounds in surgical smokes [6, 8, 11–13]. Before semiquantifying the surgical smoke generated during abdominal surgery, we analyzed the stain components on the filter paper and compared the results with those of the absorptive membrane using a mass spectrometer. The stains on the filter paper contained various harmful chemical compounds, such as acetaldehyde, dimethylformamide, and furfural, which are all known to contain carbon, and the results were in agreement with those of the absorptive membrane. With regard to the objective evaluation of residual smoke, in HF-ESU challenge, we semiquantified the residual smoke in the abdominal cavity by using the industrial smoke-analysis device. The lesser staining the evacuator group indicated the effectiveness of instantaneous smoke evacuation during ablation, which also enhanced laparoscopic visualization. In contrast, the high stain concentration in the control group reflected a sizeable volume of surgical smoke that spread into the operating room. These data may motivate laparoscopic surgeons to retrofit the operating rooms with smoke evacuators. On the other hand, we could not demonstrate any difference in the stains in LCS challenge, when LCS showed a "clean" tissue pad. This finding indicates negligible mist

production when LCS was activated without burnt sludge on the pad. The stains, however, were significantly less in the evacuator group when sludge in the crotch was evident in the LCS. This change was due to increased mist production in the presence of "dirty" tissue pads (data not shown). These results are in agreement with our subjective findings in daily laparoscopic practice: further deterioration of visualization after repeated use of LCS without cleaning the tip. These results indicate that the use of automatic smoke evacuator also would be effective in cases with heavy use of LCS, e.g., extensive laparoscopic lymph node dissection. Stains on the membranes of retrofitted closed circuits (Fig. 3C, left side) reflect the amount of harmful substances spread into operating rooms not fitted with smoke evacuators.

We agree that this study has some limitations as follows. First, this study was performed in experimental animal settings. Chemical compounds generated by activation of energy devices in our setting would have some differences from those obtained at daily practice. Second, although the smoke tester was established device in industry, there is no evidence that the tester could be adapted for evaluation of surgical smokes. Third, the IES2 is a small sample of commercially available smoke evacuators, and we have not tested other evacuators. However, in HF-ESU challenge, the fact that subjective and objective evaluations of visualization were well correlated allows us to perform further experiments. Laparoscopic surgery is performed in the abdominal cavity isolated from room air. This indicates that it is important to filter the smoke-related harmful substances for both the patients and operating room personnel using automatic smoke evacuators. There is no doubt that the smoke evacuators available in the market need further refinement especially with regard to the activation mechanisms. For example, the IES2 only interlocks with the VIO300D electrically. Ideally, smoke evacuation should be triggered automatically by sensors that detect the surgical smoke. To help the biomedical industry manufacture such devices, we need to know the components of surgical smoke and new electrochemical sensors. In addition, the algorithm of the IES2 after activation has a space to improvement. As shown in Fig. 2B and Movie 1, visualization of surgical fields have no difference in 10 s after activation of a HF-ESU suggests that smoke evacuators should be in maximum output more rapidly. These data should be feedback to medical equipment manufacturers to develop the ideal evacuator.

Conclusions

The results of the present study demonstrated that the use of automatic smoke evacuators enhanced the field-of-view and reduced exposure to harmful compounds and the surgical smoke generated during electrosurgery in experimental laparoscopic surgery. Further studies are necessary to validate the effectiveness of such devices in the clinical settings.

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Impact of reconstruction method on visceral fat change after distal gastrectomy: Results from a randomized controlled trial comparing Billroth I reconstruction and Roux-en-Y reconstruction

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Background. *Visceral fat is one of the causes of metabolic syndrome. Among the various types of bariatric surgery, duodenal–jejunal bypass is one of the most common procedures. However, the effect of duodenal bypass on fat changes is not completely understood. We examined the effect of duodenal bypass on visceral fat changes by comparing Billroth I (BI) and roux-en Y (RY) reconstruction in distal gastrectomy.*

Methods. *This retrospective study used data from 221 patients registered for a prospective randomized trial that compared BI to RY in distal gastrectomy with lymphadenectomy to treat gastric cancer. With a software package, we first quantified the visceral fat area (VFA) on cross-sectional computed tomography scans obtained at the level of the umbilicus before and 1 year after surgery, and then determined the impact of duodenal bypass on visceral fat changes.*

Results. *Clinicopathological background data did not differ between BI and RY. Rates of BMI reduction for BI and RY also did not differ. The VFA reduction rate for RY (47.2 ± 25.5%) was greater than for BI (36.8 ± 34.2%,* P = *.0104). Adjuvant chemotherapy (chemotherapy versus no chemotherapy,* P = *.0136), type of reconstruction (BI versus RY,* P < *.0001), and pathologic stage (p stage I versus p stage II–IV,* P = *.0468) correlated significantly with postoperative visceral fat loss. Multivariate logistic regression analysis identified reconstruction (BI versus RY,* P = *.0078) as a significant determinant of visceral fat loss.*

Conclusion. *Visceral fat loss after distal gastrectomy was greater for RY than for BI, and duodenal bypass may be associated with reduction of visceral fat. (Surgery 2014;155:424-31.)*

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IT HAS BEEN PROVEN that gastric bypass surgery affects the release of gastrointestinal hormones[1] and induces malabsorption,[2] but there are no conclusive data about the effects of duodenal bypass on visceral fat changes. There are various types of bariatric procedures, including gastric banding, sleeve gastrectomy, roux-en Y bypass, biliopancreatic diversion with duodenal switch, and duodenal-jejunal bypass. However, to the best of our knowledge, no authors have evaluated fat reduction specifically caused by duodenal bypass because the size of the remnant stomach and the

length of the jejunal bypass differ among the various procedures.

The selection of the reconstruction method, either Billroth I (BI) or roux-en Y (RY), after distal or subtotal gastrectomy is still controversial. A large, multi-institutional, randomized controlled trial was conducted by the Osaka University Clinical Research Group for Gastroenterological Study (Japan)[3,4] to address this problem. The primary endpoint of this study was to compare body weight loss 1 year after surgery between the BI and RY groups. Secondary endpoints were postoperative complications, nutritional state, and quality of life. This trial gave us an opportunity to prospectively evaluate data about the effects of BI and RY on visceral and subcutaneous fat loss because patients whose remnant stomachs were large enough so that either technique could be performed were assigned randomly intraoperatively to undergo either BI and RY, and the reconstruction methods were prescribed by the protocol.

Visceral fat areas (VFAs) estimated from a single computed tomography (CT) scan at the level of the umbilicus are known to correlate with the total volume of visceral fat.[5,6] On the basis of this knowledge, a practical, standardized technique has been developed to determine the VFA from a single CT scan.[7]

In the present study, we used CT and a software package to quantify the VFA of patients before and 1 year after surgery. We then determined the impact of the type of reconstructive procedure on visceral fat changes in patients with gastric cancer who underwent distal gastrectomy with lymphadenectomy.

METHODS

Patients. Between May 2004 and October 2009, a total of 332 patients with gastric cancer were registered in the original study. After completion of the informed consent process, patients were included in the study if they met the eligibility criteria.[4] After initial laparotomy, the location of the tumor was confirmed to be in the middle or lower third of the stomach and the proportion of residual stomach was regulated as one-third of the original stomach. The operator also checked the length of the residual stomach to confirm that either reconstruction procedure could be performed after distal gastrectomy. The surgeon confirmed the eligibility and exclusion criteria immediately after the initial laparotomy, and patients were then randomized intraoperatively to either the BI group or the RY group. Randomization was performed by the minimization method according to the patient's body mass index (BMI) (<25 or ≥ 25 kg/m^2) and institution.

To evaluate visceral fat changes, we collected CT scans both before and 1 year after surgery. A total of 221 patients, whose CT scans at the umbilicus level both before and 1 year after surgery could be obtained, were retrospectively analyzed in this study. Information about the patients' backgrounds and clinicopathological data were extracted from the data collected by the original study. This study was approved by the institutional review boards of all participating hospitals and was conducted in accordance with the Declaration of Helsinki.

Operative procedure. Patients underwent gastrectomy with systematic lymphadenectomy at 18 high-volume institutions in Osaka, Japan. All 18 institutions were participants in the surgical study group "Osaka University Clinical Research Group for Gastroenterological Study." Overall, more than 50 gastrectomies were performed each year in these 18 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of the reconstructive procedures.

Endotracheal general anesthesia and standard laparotomy or laparoscopic operations were used for all patients in each institution. Gastric tumors located in the lower or middle third of the stomach were treated with distal gastrectomy. Lymphadenectomy approaches were categorized as D1–3, as defined by the Japanese Classification for Standard Dissection.[8] D1 involves dissecting the paragastric nodes, whereas D2 also includes dissection of the nodes along the left gastric, common hepatic, and celiac arteries. D3 includes the nodes dissected in D1 and D2, as well as dissection of the hepatoduodenal and retropancreatic nodes, the nodes along the superior mesenteric vein, and the para-aortic nodes between the level of the celiac axis and the inferior mesenteric artery.

For BI reconstruction, the duodenum and remnant stomach were sutured. For RY reconstruction, the jejunum was divided 20 cm distal to the ligament of Treitz, and the portion of the jejunum closest to the patient's head was closed, followed by the remaining gastric pouch, which was anastomosed to the jejunum. The oral portion of the jejunum was then anastomosed to the mid-jejunum 30 cm distal to the gastrojejunostomy.