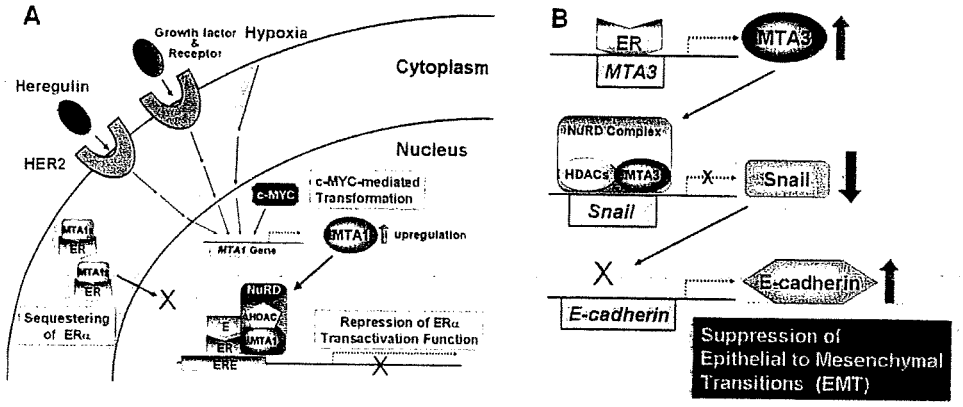

Fig. 2 Roles of MTA family in the carcinogenesis and cancer progression. Schematic presentation of the main functions of MTA family proteins. **a** MTA1 protein is included in NuRD complex that represses the transactivation function of estrogen receptor (*ER*) α, rendering breast cancer cells more phenotypically aggressive. MTA1 protein in NuRD complexes is one of the first downstream targets of c-MYC function, and it is essential for the transformation potential of c-MYC. MTA1s is a splice-variant of MTA1 that localizes in the cytoplasm where it sequesters *ERα*, resulting in the prevention of the ligand-induced nuclear translocation of ERα and stimulation of the development of the malignant phenotype of breast cancer cells. **b** MTA3 protein induced by estrogen represses the expression of the transcriptional repressor Snail, a master regulator of "epithelial to mesenchymal transitions", resulting in the expression of the cell adhesion molecule E-cadherin and maintenance of a differentiated, normal epithelial status in breast cells

Mi-2/NuRD transcriptional corepressor in breast epithelial cells [15]. The absence of MTA3 as well as the absence of ER results in an aberrantly increased expression of the transcriptional repressor Snail, a master regulator of epithelial-to-mesenchymal transitions (EMT). This increased expression of Snail results in reduction of the cell adhesion molecule E-cadherin expression and subsequently changes in epithelial architecture and invasive growth (Fig. 2b). MTA3 is a transcriptional target of ERα, and in the presence of estrogen, ERα directly binds to the MTA3 promoter at the SP1 site in close proximity of the ERE half-site, resulting in stimulation of MTA3 transcription [59, 60]. Thus, MTA3 functions to maintain a differentiated, normal epithelial status in breast cells, which is in stark contrast to MTA1 or MTA1s. Any potential up-regulation of MTA1 may repress MTA3 expression through repression of the ERα function, leading to up-regulation of Snail, down-regulation of E-cadherin, promotion of EMT and consequently an increase in metastatic potential in breast cancer cells. In fact, Mishra et al. [59] reported that MTA3 gene expression was regulated by the endogenous MTA1 and the knockdown of MTA1 resulted in a significant increase in both basal and estrogen-induced promoter activity of the MTA3 gene. Furthermore, Fujita et al. [60] revealed that a transient forced expression of MTA1 lead to loss of MTA3 protein in breast cancer cell lines. Interestingly, the same phenomenon was also observed in ovarian cancer cell line, in which MTA1 overexpression resulted in down-regulation of E-cadherin and MTA3 expression and enhanced expression of the Snail and Slug [34].

The expression of MTA3 inhibits ductal branching in virgin and pregnant mammary glands in MTA3-transgenic mice [61]. This property is in contrast to MTA1-transgenic mice, where the inappropriate development of mammary glands results in the development of hyperplastic nodules and mammary tumors, including adenocarcinomas and lymphomas [8, 40]. MTA3 also represses Wnt4 transcription and Wnt4 secretion, inhibiting Wnt-target genes in mammary epithelial cells. This repression of Wnt4 transcription was found to be mediated through a MTA3-NuRD complex, which interacts with the Wnt4-containing chromatin in an HDAC-dependent manner [61].

Although the fundamental functions of MTA proteins are exerted via transcriptional repression by histone deacetylation, a transcriptional activating function has also been demonstrated. Gururaj et al. [62, 63] showed that Breast Cancer Amplified Sequence (BCAS) 3, a gene amplified and overexpressed in breast cancers, was a chromatin target of MTA1, and the transcription of BCAS3 was stimulated by MTA1. This suggested that MTA1 has a transcriptional coactivator function in addition to a corepressor function. A similar finding has also been suggested for mouse Mta2 protein [64].

Deacetylation of non-histone proteins by the MTA family

The protein targets for deacetylation by HDAC via NuRD complexes containing MTA proteins are not only the chromatin histones but also other non-histone proteins. The tumor suppressor gene p53 product was the first non-histone protein that was reported to be deacetylated by MTA protein-containing NuRD complexes. Luo et al. [65] found that the deacetylation of p53 was mediated by a HDAC1 complex containing MTA2 protein. This MTA2-associated NuRD complex interacted with p53 in vitro and

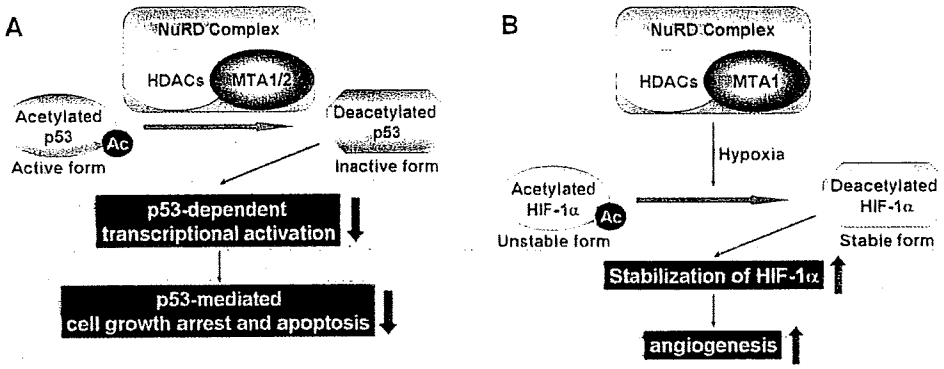

Fig. 3 Roles of MTA family in the carcinogenesis and cancer progression. Deacetylation of non-histone proteins by MTA family proteins. a Tumor suppressor p53 protein is deacetylated and inactivated by both MTA1 and MTA2 proteins in NuRD complexes, resulting in inhibition of growth arrest and apoptosis. b A hypoxia-inducible factor-1α (HIF-1α) is also deacetylated and stabilized by MTA1 protein, leading to angiogenesis

in vivo and reduced significantly the steady-state levels of acetylated p53. Deacetylation of p53 results in an increase of its own degradation through MDM2 and a reduction in p53-dependent transcriptional activation. This eventually leads to the repression of the normal p53 function that mediates cell growth arrest and apoptosis. The same phenomenon was observed between p53 and MTA1. HDAC1/MTA1 complexes possessed deacetylation activity against p53 protein in human non-small cell carcinoma and human hepatoma cells, and the complexes were found to inhibit p53-induced apoptosis by attenuating the transactivation function of p53 [66] (Fig. 3a, b).

Another important non-histone protein that is deacetylated by HDAC1/MTA1 complexes is hypoxia-inducible factor (HIF)-1α, a key regulator of angiogenic factors [67] (Fig. 3b). The expression of MTA1 is strongly induced under hypoxic conditions in breast cancer cell lines, and MTA1 overexpression enhanced the transcriptional activity and stability of HIF-1α protein. MTA1 physically binds to HIF-1α and deacetylates it by increasing the expression of HDAC1, leading to the stabilization of HIF-1α. These results indicated evidence for positive cross-talk between MTA1 and HIF-1α, which is mediated by HDAC1 recruitment. They also indicated the existence of a close connection between MTA1-associated metastasis and HIF-1α-induced tumor angiogenesis. Furthermore, Moon et al. [68] showed that MTA1 increased the transcriptional activity of HIF-1α and the expression of vascular endothelial growth factor (VEGF), a target molecule of HIF-1α. Conditioned medium collected from MTA1 transfectants increased angiogenesis in vitro and in vivo. This functional link between HIF-1α and MTA1 has been demonstrated in clinical samples of pancreatic carcinoma. Using immunohistochemistry and surgically resected pancreatic carcinomas, Miyake et al. [28] examined the expression of HIF-1α, HDAC1 and MTA1 proteins and suggested that HIF-1α expression, which is associated with a poor prognosis in patients with pancreatic cancers, might be regulated by HDAC1/MTA1 complexes. The contribution of MTA1 protein to tumor angiogenesis was also demonstrated in human breast cancers. Using immunohistochemistry, Jang et al. [19] examined MTA1 protein expression and intra-tumoral microvessel density (MVD) in clinical samples of breast cancer and showed that MTA1 expression was significantly correlated with higher tumor grade and higher tumor MVD. The relationship between MTA1 expression and MVD was also observed in HBV-associated HCC [30]. Recently, Yoo et al. [69] experimentally demonstrated that HBV-X (HBx) protein strongly induced the expressions of MTA1 and HDAC1, resulting in those physical link to HIF-1α. This suggests that positive crosstalk between HBx and MTA1/HDAC1 complex occurs and may be important in stabilizing HIF-1α, which could play a critical role in angiogenesis and metastasis of HBV-associated HCC [69].

The protein members of NuRD complexes, including MTA1 and MTA2 proteins are co-immunoprecipitated with the ataxia teleangiectasia mutated (ATM)- and Rad3-related protein (ATR) [70]. ATR is a phosphatidylinositol—kinase-related kinase that has been implicated in the response of human cells to multiple forms of DNA damage and may play a role in the DNA replication checkpoint. This fact suggests that MTA proteins may contribute to the regulation of DNA checkpoints.

Other possible functions of MTA proteins in cancer

There are other reports suggesting the possible roles of MTA proteins in carcinogenesis and cancer progression. Among them, the most important may be the relationship of MTA1 protein with c-MYC oncoprotein (Fig. 2a). By expression profiling, Zhang et al. [71] identified MTA1 protein as a

target of the c-MYC protein in primary human cancer cells and showed that c-MYC binds to the genomic MTA1 locus and recruits transcriptional coactivators. They also presented data suggesting that MTA1 protein in NuRD complexes was one of the first downstream targets of c-MYC function, essential for the transformation potential of c-MYC, because reduction of MTA1 expression by a short hairpin RNA blocked the ability of c-MYC to transform mammalian cells [71]. There are little data at present concerning the relationship between MTA1 and other important oncogene products such as c-JUN and c-FOS.

As mentioned above, Kumar's group established transgenic mice that overexpressed MTA1 protein and found that the MTA1-transgenic mice showed inappropriate development of mammary glands. These mice also developed hyperplastic nodules and mammary tumors [40]. In this study, the underlying molecular mechanisms were also examined, and the results suggested that MTA1 dysregulation in mammary epithelium and cancer cells triggered down-regulation of the progesterone receptor-B isoform and up-regulation of the progesterone receptor-A isoform, resulting in the up-regulation of the progesterone receptor-A target genes Bcl-XL and cyclin D1 in mammary glands of virgin mice. It would be extremely intriguing and important to examine the HIF-1α/VEGF expressions and angiogenesis in various organs of the MTA1-transgenic mice, although there are no data concerning these questions at present.

Recently, Molli et al. [72] reported that MTA1/NuRD complexes negatively regulated BRCA1 transcription by physically associating with ERE of the BRCA1 promoter in an ERα-dependent manner and that this repressive effect of MTA1 on BRCA1 expression resulted in an abnormal centrosome number and chromosomal instability. The relationship of MTA proteins with tumor suppressor genes other than p53 and BRCA1 remains to be determined.

Our group showed by the yeast two-hybrid system that mouse Mta1 protein physically linked to endophilin 3 and that the binding of those proteins was made between the SH 3-binding domain of Mta1 protein and the SH-3 domain of endophilin 3 [73]. This suggested that MTA1 protein might be involved in the regulation of endocytosis mediated by endophilin 3.

MTA proteins as new molecular targets: clinical implications

On the basis of the available data discussed briefly in this review, it is very likely that MTA proteins have important and critical roles in the genesis and progression of a wide variety of cancers [74]. MTA1 protein can be thought of as a master co-regulatory molecule, strongly and clearly suggesting the possibility that MTA1 protein (or its gene) could be an excellent molecular target for cancer therapy as well as its use in cancer diagnosis/prognosis. Although studies are not yet available which show the "clinical" efficacy of targeting MTA proteins, several experiments have shown that MTA1 protein (or its gene) could be a molecular target for cancer therapy.

The first studies that suggested the possibility of targeting MTA1 were reported by Nawa et al. [3] and Nicolson et al. [74]. They used antisense phosphorothioate oligonucleotides against *MTA1* mRNA and found a growth inhibitory effect on human metastatic breast cancer cell lines. Since these reports, others have shown that inhibition of MTA1 expression can result in the inhibition of the malignant phenotypes of various cancers, as mentioned below.

Various techniques have been used to regulate MTA1 expression. Using RNAi, Qian et al. [43] inhibited MTA1 expression in a human esophageal squamous cell carcinoma cell line and demonstrated significant inhibition of in vitro invasion and migration properties of the cancer cells. The same group further examined the therapeutic value of MTA1 levels in malignant melanoma cells and demonstrated that down-regulation of MTA1 by RNAi successfully suppressed the growth in vitro and experimental metastasis of mouse B16F10 melanoma cells in vivo, suggesting a promising use of the *MTA1* gene as a target for cancer gene therapy [75].

MTA1s may also be a useful target in the treatment of breast cancer. MTA1s functions as a repressor of ERα transcriptional activity by binding and sequestering the ERα in the cytoplasm [16]. MTA1s has a unique C-terminal 33-amino acid region containing a nuclear receptor-box motif that mediates the interaction of MTA1s and ERα. Singh et al. [76] showed that the MTA1s peptide containing this motif could effectively repress the ERα transactivation function, estrogen-induced proliferation and anchorage-independent growth of the human breast cancer cell line MCF-7. Using an animal model, they also showed the effect of MTA1s peptide in blocking the tumor progression of MCF-7 overexpressing ERα.

There is a good possibility that MTA1 will be a target of immunotherapy. In a review on a model for immunotherapy using a vector, disabled infectious single cycle-herpes simplex virus (DISC-HSV), Assudani et al. [77] proposed that MTA1 is a promising antigen for tumor rejection, because it is greatly overexpressed in many different tumors and is only expressed at lower levels in normal tissues. Their initial studies demonstrated the presence of immunogenic MHC class I-restricted peptides of MTA1. Furthermore, MTA1 was identified as a SEREX antigen, and hence it is likely to be capable of inducing a T-cell response in cancer patients [78].

Conclusions and future directions

This review has focused on the clinical and biological significance of the newly emerging gene family named MTA, paying particular attention to its relevance to carcinogenesis and cancer progression, such as invasion and metastasis. The fundamental roles of MTA proteins are thought to be transcriptional corepressors that function through histone deacetylation via NuRD complexes, which contain chromatin remodeling and histone deacetylating molecules. Repression of ERα transactivation function by MTA1 protein through deacetylation of ERE chromatin of the ER-responsive genes has been the most extensively investigated, and the data clearly demonstrate that MTA1 expression results in tumor formation in mammary glands and renders breast cancer cells phenotypically more aggressive. In addition, MTA proteins deacetylate non-histone proteins. For example, the tumor suppressor p53 protein is deacetylated and inactivated by both MTA1 and MTA2 proteins, resulting in inhibition of growth arrest and apoptosis. HIF-1α is also deacetylated and stabilized by MTA1, leading to angiogenesis. Considering the many reports showing the clinical relevance of the expression of *MTA1* mRNA and its encoded protein in a wide variety of human cancers as well as definitive studies showing the molecular and biochemical mechanisms of MTA protein actions, it is likely that MTA proteins, especially MTA1, represent master co-regulatory molecules involved in the carcinogenesis and progression of various malignant tumors. Ultimately this will lead to clinical applications of MTA proteins as a new class of molecular targets for cancer therapy. For example, inhibition of MTA1 expression or function may enhance the chemosensitivity of cancer cells by restoring tumor suppressor function of p53, or it may inhibit tumor angiogenesis by destabilizing the angiogenesis promoting function of HIF-1α. Moreover, inhibitors of MTA proteins may cooperate with HDAC inhibitors, which are now expected to be a new class of anticancer agents. MTA1 will also be clinically useful for the prediction of the malignant potentials of various human cancers, such as esophageal, gastric and colorectal cancers. Thus, evaluating the expression levels of MTA proteins in individual cases of various cancers may provide clinicians with important clues to prognosis and anticancer therapy.

It will be important to understand the physiological functions and underlying mechanisms of MTA proteins in normal cells, because MTA proteins are also expressed in normal cells and tissues, although at lower levels than found in cancer cells. Physiological roles of MTA1 reported are the followings: (1) MTA1 is thought to play a crucial role in postnatal testis development and spermatogenesis [79, 80], (2) The expression level of MTA1 decreases in mouse brain in age-dependent manner, which influences the estrogen-mediated signaling pathway during aging [81], (3) MTA1 protein is a direct stimulator of rhodopsin expression [82], (4) MTA1 stimulates hepatic proliferation in vivo and hepatocyte differentiation in vitro [83]. Furthermore, *Caenorhabditis elegans* has MTA1 homologues, egl-27 and egr-1, which are related to embryonic patterning [11, 84] and NURD complex including egr-1 antagonizes vulval development of *C. elegans*, which is induced by Ras signal transduction pathway [85]. Thus, understanding the physiological functions of MTA proteins will be absolutely necessary to understand the pathological functions of MTA proteins in human cancers. It will be also important to understand MTA1's roles in tissue maintenance via HIF-1α/VEGF expressions against hypoxic condition.

In conclusion, MTA proteins, especially MTA1, are undoubtedly excellent candidates for therapy and diagnosis/prognosis of human cancers and should be intensively studied for their possible clinical applications.

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ORIGINAL ARTICLE

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Evaluation of the feasibility and safety of immediate extubation after esophagectomy with extended radical three-field lymph node dissection for thoracic esophageal cancers

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Abstract
Background. No standard procedure exists in respiratory management, including mechanical ventilation, which is commonly administered, after thoracic esophagectomy for esophageal cancer.
Methods. Various perioperative clinical parameters and complications were retrospectively compared between the patients who underwent mechanical ventilation (MV group, $n = 38$) and those who were extubated immediately (immediate extubation: IE group, $n = 75$), following transthoracic esophagectomy with three-field lymph node dissection (3FLND) for thoracic esophageal cancers.
Results. There were no significant differences between the two groups in the early postoperative clinical course. The frequencies of postoperative complications were 39% and 47% in the IE and MV groups, respectively, and pulmonary complications tended to occur more frequently in the MV group (23.7%) than in the IE group (12.0%). Mobilization of the patients was significantly earlier in the IE group than in the MV group ($P < 0.0001$).
Conclusions. IE is feasible and safe even after transthoracic esophagectomy with 3FLND. To avoid the possible disadvantages of MV after surgery, IE can be a standard protocol for postoperative management after transthoracic esophagectomy with radical lymph node dissection.

Key words Esophageal cancer · Esophagectomy with three-field lymph node dissection · Immediate extubation · Mechanical ventilation · Postoperative complications

Introduction

In spite of recent advances in perioperative managements of radical esophagectomy for thoracic esophageal cancers, morbidity and mortality remain high, even in centers that perform a high volume of esophagectomies [1–5], because (1) patients with esophageal cancers frequently have some underlying complications before surgery, including malnutrition caused by dysphagia, (2) many of the patients are elderly and tend to have significant comorbidities, and (3) resection of thoracic esophageal cancers inflicts considerable physiological stress. Especially, as the extent of the surgical stress of transthoracic esophagectomy with cervical, mediastinal, and abdominal (so-called three-field) lymph node dissection (3FLND) is thought to be extremely great [6–8], careful perioperative management is mandatory. However, no standard protocol for this management has yet been established.

Respiratory complications are the primary cause of morbidity and mortality after esophageal surgery [9,10]. Adult respiratory distress syndrome (ARDS), a major contributor to respiratory complications after esophagectomy, causes a high postoperative death rate [11,12]. To avoid this severe complication, the patients are commonly managed under artificial mechanical ventilation (MV) for one or several days after surgery in many institutes, on the assumption that this may minimize the occurrence of respiratory complications. However, the duration and intensity of MV for patients after esophagectomy vary among institutes, and thus no optimal procedure for respiratory management has yet been established. In addition, there is little clear evidence for the necessity of MV itself.

On the other hand, there is increasing evidence that MV is potentially harmful even for a short period [13–15]. Ventilator-induced pulmonary edema can cause pulmonary changes similar to ARDS, as often occurs in patients after transthoracic esophagectomy, because one-lung ventilation is required during a thoracotomy that is associated with the development of microbarotrauma in the dependent lung and with organ reperfusion injury in the collapsed lung [11,16,17]. Thus, latent damage might already exist in the lungs at the end of transthoracic esophagectomy and MV continued after esophagectomy itself may therefore be harmful rather than useful.

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Recently, some surgical teams have demonstrated the efficacy of postoperative immediate extubation (IE) following an esophageal resection, most of which are Ivor-Lewis, transhiatal, or left thoracoabdominal esophagectomies with limited lymph node dissection [18–22]. However, very few reports have showed the feasibility and safety of this practice for patients with thoracic esophageal cancers who underwent transthoracic esophagectomy with extended radical 3FLND. The current study compared the early postoperative clinical course and morbidity and mortality rates between the patients with and without IE following this kind of radical surgery in this institution and evaluated the feasibility and safety of IE.

Patients and methods

Patients

During the period from 2002 to 2007, 165 patients with esophageal cancer underwent surgery in the National Kyushu Cancer Center, Japan. All cancers were pathologically diagnosed to be squamous cell carcinoma. Among them, 117 patients with thoracic esophageal cancer underwent transthoracic esophagectomy with 3FLND, basically by the same surgical procedures. Thirty-eight patients up to 2003 were managed under MV shortly after their esophagectomy (MV group). The average length of MV was 9.9 h. To avoid possible risks related to MV, the time length of postoperative MV in the surgical ward was gradually shortened during a period of 4 years from 2000 to 2003, and the policy of postoperative MV was finally changed to IE in the operating room in January 2004. Among the 79 patients after 2004, 75 were thus immediately extubated after the esophagectomy in the operating room (IE, immediate extubation group), unless there were specific contraindications. These 38 patients of the MV group and 75 patients of the IE group were included in this study.

Preoperative assessment and management

All patients underwent a full blood count, serum biochemistry, electrocardiogram, chest X-ray, and pulmonary function tests including forced vital capacity (FVC, %VC) and forced expiratory volume in the first second (FEV1.0, % FEV1.0). A blood gas analysis was also performed.

Preoperative staging of the thoracic esophageal cancer was conducted by esophagography, upper gastrointestinal endoscopy, computed tomography (CT) of the cervix, chest, and abdomen, ultrasonography of the cervix and abdomen, and bone scintigraphy. ^{18}F-Fluorodeoxyglucose-positron emission tomography (FDG-PET) was also used for some of the patients.

For the patients whose tumor was suspected to have directly invaded adjacent organs such as the aorta, trachea, and bronchus (i.e., T4 tumor), neoadjuvant therapy including chemotherapy by CDDP + 5-FU and concurrent irradiation of 30 Gy was administered. Preoperative nutritional support was given to patients with severe dysphagia and malnutrition by intravenous hyperalimentation.

Anesthesia

General anesthesia using oxygen and an inhalational agent, combined with an epidural anesthesia sited in the low thoracic position (T9–T10 to T11–T12), was performed. Just before the start of the surgical procedure, 250 mg hydrocortisone was administered intravenously.

During the procedures through right thoracotomy, one-lung mechanical ventilation with a double-lumen tracheal tube was undertaken with occasional assistance of high-frequency jet ventilation, if necessary.

The main criteria for IE were based on the judgment of the anesthesiologists when (1) the patient had no major preoperative and/or intraoperative cardiopulmonary complications, (2) the neuromuscular blockade was resolved and the patient was awake, (3) spontaneous respiration and tidal volume were adequate (respiratory rate < 30/min, tidal volume > 5 ml/kg), (4) blood gas analysis was good (>98% of SpO_2 at FiO_2 <0.4) just before extubation, and (5) adequate cough during suctioning.

Surgical procedure

All 117 patients underwent transthoracic esophagectomy through a right-side thoracotomy. The alimentary tract was reconstructed using a gastric tube made of the greater curvature of the stomach, with cervical esophagogastric anastomosis by hand-sewn or instrumental anastomosis through a retrosternal or posterior mediastinal route. For the thoracotomy, a skin incision about 10–12 cm long was made and the thoracic cavity was entered through the fourth or fifth intercostal space using a muscle-preserving splitting method and without fracture of any ribs. The transthoracic procedures were performed with thoracoscopic assistance.

An extended radical lymph node dissection was then performed in three fields. Through the right thoracotomy, complete dissection of the middle and lower mediastinal nodes included the periesophageal, parahiatal, subcarinal, and aortopulmonary window nodes. Dissection of the lymph nodes in the upper mediastinum included the nodes along the bilateral recurrent laryngeal nerves by carefully exposing them, from the level of the aortic arch to the thoracic inlet for the left nerve and near the origin at the base of the right subclavian artery for the right nerve. Through a cervical U-shaped incision, the reminder of the nodes along the recurrent laryngeal nerves, which were anatomically inseparable chains extending from the upper mediastinum to the lower neck, were also dissected, together with the lower deep cervical nodes located posterior and lateral to the carotid sheath. Lymph node dissection in the abdomen included the nodes along the celiac, left gastric, and common hepatic arteries, the nodes along the lesser curvature of the stomach, and the parahiatal nodes.

Postoperative management

After surgery, the patients were transferred to the surgical ward (until November 2005) or the newly equipped intensive care unit (after December 2005) of the hospital. Postoperative analgesia was continued with an epidural infusion using a patient-controlled analgesia system for several days. Most patients intravenously received pentazocine and/or nonsteroidal analgesia, if not contraindicated, depending on the patients' wishes. Also, 125 mg hydrocortisone was intravenously administered on postoperative day (POD) 1 and POD 2.

The patients were urged to be mobilized in the hall with assistance of nurses several times on POD 1. The thoracic drain was removed when the amount of the discharge became less than 100 ml per day.

Oral diet intake was resumed on POD 7. Parenteral nutritional support was continued until adequate oral intake was achieved. Postoperative mandatory nutrition via feeding tube was not performed in either group.

Data analyses and statistics

All the statistical analyses were performed by using the StatView software program (version 5.0; Abacus Concepts, Berkeley, CA, USA). The early postoperative clinical course was compared between the MV and IE groups. Data included body temperature, pulse rate, urine volume, peripheral white blood cell and lymphocyte counts, C-reactive protein (CRP), and PaO_2; differences were analyzed by Student's t test or the chi-square test. The occurrence of postoperative complications, timing of mobilization and removal of the thoracic drain, and the length of the postoperative hospital stay were also compared between the two groups; differences were evaluated by Mann–Whitney's U test. $P < 0.05$ was considered statistically significant.

Results

The clinical characteristics of both MV and IE groups are shown in Table 1. Among the 79 patients after 2004 who underwent transthoracic esophagectomy with 3FLND, 75 (94.9%) were immediately extubated after the esophagectomy in the operating room. The remaining 4 patients were managed under postoperative MV, including (1) a patient whose right lung was seriously injured during surgery because of marked adhesion of the pleura, (2) a patient who showed severe laryngeal spasm and choking 15 min after IE and was then reintubated, and (3) 2 patients who did not clear the respiratory function criteria described above.

There were no differences in age, sex, performance status, preoperative comorbidities, percentage of patients receiving neoadjuvant chemoradiotherapy, preoperative respiratory function (%VC and FEV1.0%), and pathological stage between the MV and IE groups. However, the average operation time, one-lung ventilation time, and anesthesia time were significantly shorter in the IE group than those in the MV group. These differences were attributed to the gradual and steady improvement in the technical skills of both the surgeons and the surgical team, because the surgical procedures, such as the methods for thoracotomy and extent of lymph node dissection, were basically the same between the two groups investigated in this study. All patients were preoperative ASA grade II or less, and no differences existed between the two groups.

Figure 1 shows comparisons of early postoperative clinical course values between the MV and IE groups. There were no significant differences in the changes in the vital clinical parameters during the first 72 h after surgery, including body temperature, pulse rate, urine volume, and PaO_2. Although the changes of the peripheral white blood cell and lymphocyte counts and CRP value during the 7 days after the operation were not significantly different between the two groups, the lymphocyte count recovered more rapidly

Table 1. Patient characteristics

Characteristic	IE ($n = 75$)	MV ($n = 38$)	P
Age (years)	63.2 ± 7.3	63.1 ± 9.0	NS
Sex (male/female)	59/16	33/5	NS
PS (0/1/2)	50/24/1	27/11/0	NS
Comorbidity (%)	41 (54.7)	21 (55.3)	NS
NeoCRTx (%)	17 (22.7)	13 (34.7)	NS
Respiratory function			
%VC	112.7 ± 14.2	111.4 ± 14.0	NS
FEV 1.0%	74.9 ± 8.0	75.6 ± 8.7	NS
Operation time (min)	531 ± 77	615 ± 74	<0.0001
OLV time (min)	213 ± 52	256 ± 68	<0.0005
Anesthesia time (min)	639 ± 74	699 ± 68	<0.0001
Blood loss (g)	507 ± 343	824 ± 545	<0.0005
pStageI/II/III/IV (n)	23/29/14/9	10/12/8/8	NS

IE, immediate extubation; MV, mechanical ventilation; NS, not significant; PS, ECOG Performance Status; neoCRTx, neoadjuvant chemoradiotherapy; VC, ventilatory capacity; OLV, one-lung ventilation
The pStage is according to the Japan Esophageal Society [29]
Some data are presented by mean ± standard deviation

Table 2. Postoperative morbidity and mortality after transthoracic esophagectomy with three-field lymph node dissection

	IE ($n = 75$)	MV ($n = 38$)	P
Morbidity			
Pulmonary complication	9 (12.0)	9 (23.7)	NS
Pneumonia/ARDS	4 (5.3)	7 (18.4)	NS
Reintubation	2 (2.7)	1 (2.6)	NS
CTN insertion	2 (2.7)	1 (2.6)	NS
Usage of bronchoscopy	9 (12.0)	9 (23.7)	NS
Pleural effusion	3 (4.0)	1 (2.6)	NS
Chylothorax	1 (1.3)	–	NS
Pulmonary embolism	–	1 (2.6)	NS
RLNP	16 (21.3)	9 (23.7)	NS
Anastomotic leakage	10 (13.3)	4 (10.5)	NS
Cardiac complication	5 (6.7)	2 (5.3)	NS
Liver complication	6 (8.0)	2 (5.3)	NS
Other	11 (14.7)	5 (13.2)	NS
Any complication	29 (38.7)	18 (47.4)	NS
Mortality	1 (1.3)	–	NS

IE, immediate extubation; MV, mechanical ventilation; NS, not significant; ARDS, acute respiratory distress syndrome; CTN, cricothyroidotomy needle; RLNP, recurrent laryngeal nerve palsy (%)

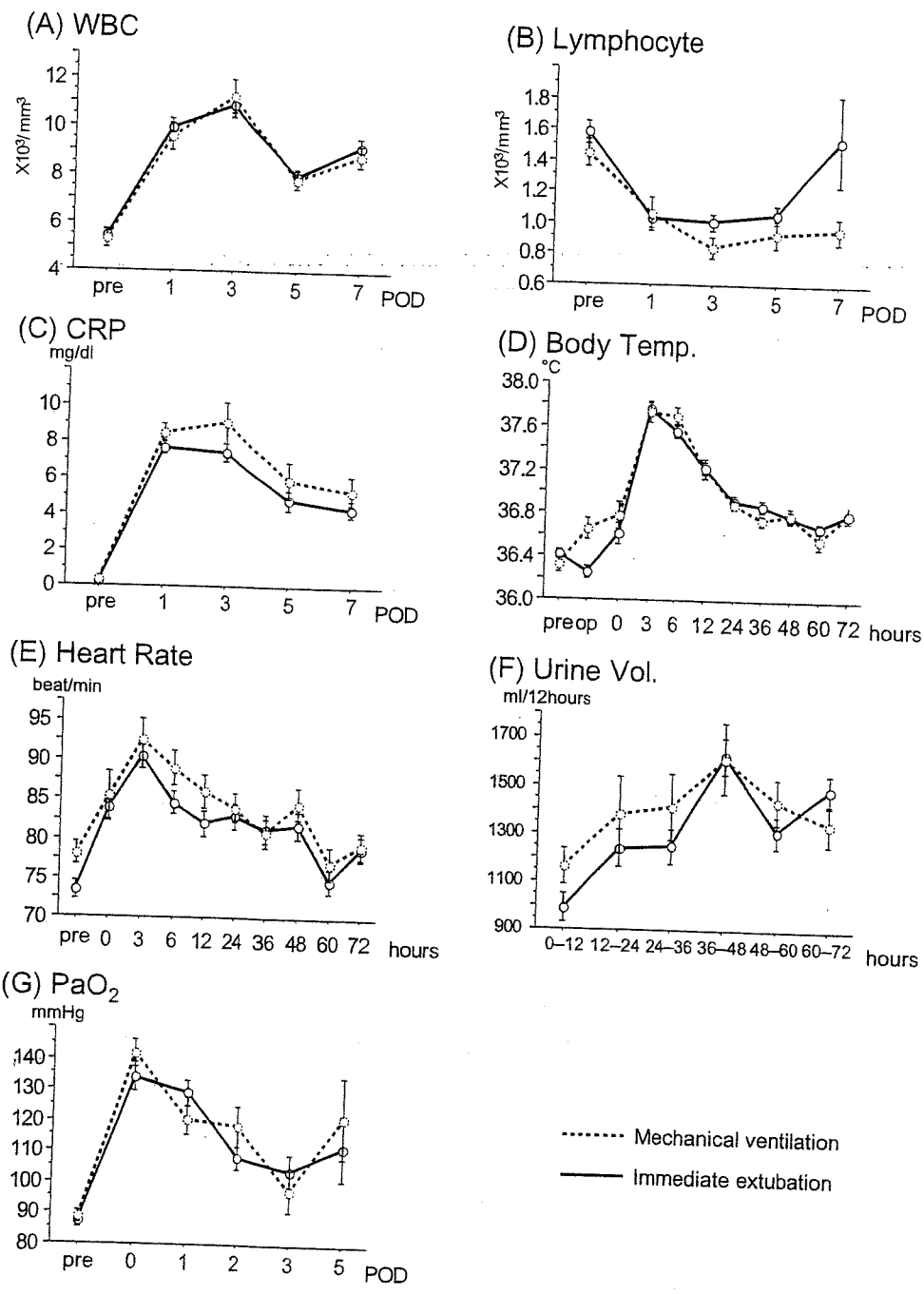

Fig. 1. Comparison of early postoperative clinical parameters between the IE (immediate extubation) and MV (mechanical ventilation) groups: white blood cell count (**A**); lymphocyte count (**B**); CRP (C-reactive protein) (**C**); body temperature (**D**); heart rate (**E**); urine volume (**F**); and PaO_2 (**G**). *Solid and dashed lines* represent the IE and MV groups, respectively; *vertical bars* indicate standard error. There were no statistical differences between the two groups in any parameter

and the CRP value was consistently lower in the IE group than in the MV group during those 7 days.

Table 2 shows the postoperative complications for which any medical and/or surgical treatments were required. Postoperative complications occurred in 38.7% (29/75) of the IE group and in 47.4% (18/38) of the MV group; this was not statistically significant. Pulmonary complications tended to occur more frequently in the MV group (9/38: 23.7%) than in the IE group (9/75: 12.0%), although the difference was not statistically significant ($P = 0.10$). Among them, reintubation or the insertion of a cricothyroidotomy needle (Trahelper; Top, Tokyo, Japan) was required to treat severe pneumonia or ARDS for 2 (2.7%) or 2 (2.7%) in the IE group, respectively, whereas these procedures were required for 1 each (2.6% each) in the MV group. Bronchoscopy for aspiration of the sputum was applied to 12.0% (8/75) and 23.7% (9/38) in the IE and MV groups, respectively. Recurrent laryngeal nerve palsy was observed in 21.3% (16/75) and 23.7% (7/38) in the IE and MV groups, respectively. Frequency of anastomotic leakage was 13.3% (10/75) and 10.5% (4/38) in the IE and MV groups, respectively, all of which could be treated conservatively. One death occurred in the IE group (1.3%), which was caused by a severe chylothorax followed by massive unexpected intracranial bleeding at POD 26. (This case was included in the patients requiring reintubation.)

Table 3. Mobilization, duration of thoracic drainage, and postoperative hospital stay

	IE ($n = 75$)	MV ($n = 38$)	P
Mobilization (POD)	1.1 ± 0.72	2.1 ± 0.39	<0.0001
Removal of TD (POD)	5.9 ± 5.8	5.8 ± 2.4	NS
Hospital stay (POD)	31.3 ± 20.3	35.8 ± 36.2	NS

Data are represented by mean ± standard deviation
IE, immediate extubation; MV, mechanical ventilation; POD, postoperative day; TD, thoracic drain

Mobilization of the patients (standing up and walking in the hall) was possible on average POD 1.1 in the IE group (95% of the patients could be mobilized on POD 1) whereas on average POD 2.1 in the MV group ($P < 0.0001$). Duration of drainage through a thoracic tube and the length of hospital stay were 5.9 and 31 days in the IE group, respectively, and 5.8 and 36 days in the MV group, respectively; the differences were not statistically significant (Table 3).

Discussion

This study demonstrated that the patients with IE after transthoracic esophagectomy with radical 3FLND showed quite a similar postoperative course to those with MV, and there were no significant differences in postoperative morbidity and mortality between the two groups. Some reports have already shown that IE after esophagectomy is safe and effective for postoperative management [18–22]. However, the esophagectomies in those studies are mostly Ivor-Lewis, transhiatal, or left thoracoabdominal esophagectomies with limited lymph node dissection. Moreover, few reported the results of comparisons in the early postoperative clinical course between patients with MV and IE. Therefore, there has been no report on this subject for more extensive transthoracic esophagectomy with radical 3FLND. In this type of surgery, more emphasis is put on the radical dissection of the lymph nodes along the recurrent laryngeal nerves, which anatomically consist of an inseparable chain extending from the upper mediastinum to the lower neck [6–8], possibly resulting in enhancement of the risks of postoperative pulmonary complications. In fact, quite high morbidity and mortality rates still continue to be reported after a 3FLND for esophageal cancer, even at specialized institutes [6–8,23,24]. Therefore, this is the first study to show the outcome of IE for patients undergoing transthoracic esophagectomy with radical 3FLND.

This study was not a prospective randomized trial, and some differences in background such as the surgical time, one-lung ventilation time, and the amount of blood loss exist between the IE and MV groups, which are thought to be the results of gradual and steady technical evolution, especially in the surgical procedures during the thoracotomy. Therefore, it is difficult to draw any definitive conclusions regarding the superiority of IE to MV in safety and feasibility. However, the morbidity and mortality rates in the IE group themselves were comparable to those from most of the institutes with a policy of elective postoperative MV [1,5,9]. Furthermore, the data in the IE group presented here are also comparable to the previous reports on IE after esophagectomies that were less extensive than the procedure with 3FLND. Those reports showed that the morbidity and mortality rates ranged from 35% to 45% and 0.3% to 8.2%, respectively, and the reintubation rate ranged from 2% to 16% [19–22]. Thus, it is unlikely that IE will increase the risk of postoperative complications, and we believe that IE can be safely performed with permissible risks. In addition, the merits of IE described below should be fully utilized, because reliable predictive indices for successful weaning after prolonged postoperative MV do not exist.

The possible merits of IE in comparison to MV after esophagectomy include avoiding the risks of pulmonary damage induced by MV and of the difficulties of weaning caused by prolonged MV. In fact, no increase in pulmonary complications was observed in the IE group in this study. Second, an emergent reintubation or tracheostomy can be more easily and safely performed in the operating room immediately after extubation, in the event of airway obstruction caused by vocal cord edema or laryngeal spasm such as in the case described in the Results. Third, IE allows mobilizing patients at an earlier stage of the postoperative course, thus leading to a decrease in morbidity such as pulmonary complications. In this institute, 95% of the patients could stand up and walk in the hall with some help on the next day after the operation, and no adverse events were observed in association with early mobilization. To facilitate IE and early mobilization, it is necessary to achieve effective postoperative analgesia [25–27]. Finally, IE after esophagectomy may help to reduce the demand on overburdened intensive care units, and subsequently the medical costs may also be reduced.

Conclusions

IE is safe and feasible even after transthoracic esophagectomy with extended radical 3FLND. To avoid the possible disadvantages of MV after surgery, IE should thus become a standard strategy for postoperative management after esophagectomy. Standardized clinical care pathways should be established, including IE after esophagectomy. Therefore, an organized institution-wide infrastructure is indispensable to optimize the outcomes in perioperative management for patients with esophageal cancer [22,28].

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ORIGINAL ARTICLE

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Follow-up and recurrence after a curative esophagectomy for patients with esophageal cancer: the first indicators for recurrence and their prognostic values

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Abstract
Background. No standardized methods exist for the follow-up and treatment of recurrence after a curative esophagectomy for patients with thoracic esophageal cancers.
Methods. One hundred seventy-five patients with thoracic esophageal cancer underwent a curative resection and were followed up during a median period of 3.0 years (3 months–18 years). The time to recurrence, the first indicators (FIs) to suspect recurrence, and the factors predictive of prognosis after recurrence were investigated.
Results. Recurrence occurred in 72 (41.1%) of 175 patients. Forty (55.6%) and 22 (30.6%) of 72 cases presented with recurrences in the first and second year after the initial operation, respectively. Clinical visit (anamnesis and physical examination), tumor markers, and imaging were FIs in 39 (54.2%), 33 (45.8%), and 49 (68.1%) of 72 patients with recurrence, respectively. Imaging was the exclusive FI in 19 (26.4%) cases. A multivariate analysis showed the favorable prognostic factors after recurrence to be recurrence later than 1 year after the initial operation and a case in which the FI was only imaging.
Conclusions. Intensive follow-up is required in the first 2 years after surgery, and early detection of recurrence is important. The accumulation of clinical data based on a fixed schedule with consensus is necessary to obtain more definite evidence for the diagnosis and treatment of recurrent esophageal cancer.

Key words Esophageal cancer · Esophagectomy · Postoperative follow-up · First indicators for recurrence · Prognostic factors after recurrence

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Introduction

Despite the recent improvement in the treatment outcome for the patients with esophageal cancer by multimodality therapy, including extensive lymph node dissection [1], postoperative recurrence is observed in a considerable number of patients [2–4]. Curative treatment of patients with recurrence is necessary to further improve the prognosis after an esophagectomy.

The guidelines for diagnosis and treatment of carcinoma of the esophagus as stated by the Japan Esophageal Society [5] separately describe methods of follow-up after the initial treatments and the treatment strategies for recurrences of each initial treatment, i.e., endoscopic resection, curative esophagectomy, and definitive chemoradiation. However, critical evidence to justify these guidelines is very limited for both the follow-up method and treatment of recurrences, and no definite guiding principles have been established in Japan. This limitation is also true in Western countries. A few recommendations for follow-up observation after surgery are noted in the guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) [6,7], although no references showing evidence are cited. Large-scale clinical studies addressing the methods of follow-up observation after treatment seem difficult to design, because the choice of the initial treatment for esophageal cancer varies markedly depending on the stage of the disease and the general condition of the patient at the time of diagnosis. Moreover, it appears to be difficult to directly adapt the data from Western countries to Japanese patients with esophageal cancers because there are large differences in the proportions of the predominant histology, in the surgical methods used, and in survival rates after surgery between Japan and the Western countries [1].

Many reports have shown the rate, timing, and mode of recurrence after a curative esophagectomy and the treatment outcomes of recurrent esophageal cancers, some of which also note the predictive factors of recurrence [2–4,8,9]. However, very few articles describing effective follow-up

methods, first clinical indicators to suspect recurrence, or factors predictive of the prognosis after the treatment of recurrence have so far been published for esophageal cancers. This study investigated the time to recurrence and predictive factors of recurrence after a curative esophagectomy with an extended lymph node dissection for esophageal cancer. Furthermore, in our study we tried to clarify the first clinical indicators to suspect recurrence and their prognostic values, using retrospective data obtained by a fixed schedule of follow-up observation in this institute. The effective postoperative follow-up strategy for patients who undergo a curative esophagectomy with an extended lymph node dissection for esophageal cancers is discussed based on the results of this study.

Patients and methods

Patients

One hundred seventy-five patients with thoracic esophageal cancer underwent a transthoracic esophagectomy with a three-field lymph node dissection with no pathological residual tumor (R0) between 1989 and 2006 in the National Kyushu Cancer Center, Japan. All cancers were pathologically diagnosed to be squamous cell carcinoma. The characteristics of the patients with and without recurrence are shown in the Results section. The median follow-up period was 3.0 years (range, 3 months–18 years).

Surgical procedure

All 175 patients underwent transthoracic esophagectomy through a right-side thoracotomy. The alimentary tract was reconstructed using a gastric tube made of the greater curvature of the stomach, with cervical esophagogastric anastomosis by hand-sewn or instrumental anastomosis [10] through a retrosternal or posterior mediastinal route.

An extended radical lymph node dissection was then performed in three fields. A complete dissection of the middle and lower mediastinal nodes was performed via a right thoracotomy, including the periesophageal, parahiatal, subcarinal, and aortopulmonary window nodes. The dissection of the lymph nodes in the upper mediastinum included the nodes along the bilateral recurrent laryngeal nerves by carefully exposing them, from the level of the aortic arch to the thoracic inlet for the left nerve and near the origin at the base of the right subclavian artery for the right nerve. The remaining nodes along the recurrent laryngeal nerves, which were anatomically inseparable chains extending from the upper mediastinum to the lower neck, were also dissected through a cervical U-shaped incision, together with the lower deep cervical nodes located posterior and lateral to the carotid sheath. The lymph node dissection in the abdomen included the nodes along the celiac, left gastric, and common hepatic arteries, the nodes along the lesser curvature of the stomach, and the parahiatal nodes.

Follow-up after surgery

The patients with a pathological stage II or higher stage [11,12] were followed up every 2 months for the first 2 years and every 3 months thereafter in the fixed schedule shown in Fig. 1. A detailed anamnesis for history and a physical examination were performed on every clinical visit. Serum levels of tumor markers including carcinoembryonic antigen (CEA: normal range, <5 ng/ml) and squamous cell carcinoma antigen (SCC-Ag: normal range, <2 ng/ml) were measured at every clinical visit. Radiologic imaging tests including cervical, chest and abdominal computed tomography (CT), and cervical and abdominal ultrasonography (US) were performed every 4 months for the first 2 years and every 6 months thereafter. CT and US were performed at the same time to complement the limitations of each imaging modality. The follow-up for the patients with pathological stage I [11,12] was less intensively performed for the first 2 years with a clinical visit and monitoring of serum levels of tumor markers at every 3 months and radiologic imaging tests at every 6 months. In addition, bone scintigraphy and gastrointestinal endoscopy were performed once a year. Positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) was indicated when recurrence was suspected. The duration of follow-up observation is set for 5 years because of the extremely low rate of recurrence later than 5 years after the initial operation.

In total, 28 patients failed to be followed up by the regular schedule. Sixteen of these patients died of other diseases during the regular follow-up and 7 dropped out of

Modality	Months after esophagectomy																							
	1st year						2nd year						3rd year				4th year				5th year			
	2	4	6	8	10	12	14	16	18	20	22	24	27	30	33	36	39	42	45	48	51	54	57	60
CV, Tumor marker	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Cervical US		●		●		●		●		●		●		●		●		●		●		●		●
Cervical–thoracic CT		●		●		●		●		●		●		●		●		●		●		●		●
Abdominal–pelvic CT		●		●		●		●		●		●		●		●		●		●		●		●
Abdominal–pelvic US		●		●		●		●		●		●		●		●		●		●		●		●
Upper GI endoscopy						●						●				●				●				●
Bone scintigraphy						●						●				●				●				●
Ba enema or Colonoscopy												●								●				

Fig. 1. Schematic representation of the follow-up schedule after a curative esophagectomy for thoracic esophageal cancer at our institute. CV, clinical visit; US, ultrasonography; CT, computed tomography; GI, gastrointestinal

Table 1. (a) Mode and rate of recurrence after a curative esophagectomy for cancer and treatment for recurrence

Mode of recurrence	No. of recurrences	Treatment (no. of patients)
Lymph node	39 (22%)	CRT (23), surgery (3) RT (5), CT (4), none (4)
Distant organ	15 (9%)	CRT (2), surgery (2) RT (5), CT (5), none (1)
Pleural dissemination	4 (2%)	CT (3), none (1)
Combined	14 (8%)	CRT (7), surgery (1) RT (1), CT (4), none (1)
Total	72 (41%)	

CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy

a regular follow-up schedule for personal reasons. The median follow-up periods were 2.2 years (0.7–6.5 years) for the former and 2.0 years (0.5–2.5 years) for the latter. Only 5 among 72 cases with recurrence were found to have recurrences before the prefixed next timing of the schedule because they showed some symptoms and signs and spontaneously visited our hospital. Their first indicators were judged to be "clinical visit." All these patients were included in the analysis.

Data analyses and statistics

All statistical analyses were performed using the StatView software program (version 5.0; Abacus Concepts, Berkeley, CA, USA). The relationship between recurrence and the clinicopathological features was determined using a Student's *t* test, Fisher's exact test, and a logistic regression analysis. Survival rates after recurrence were calculated by the Kaplan–Meier method for the analysis of censored data. The significance of differences in survival was analyzed with a log-rank test and a generalized Wilcoxon test in a univariate analysis and a Cox's proportional hazards model in a multivariate analysis. A P value < 0.05 was considered to be statistically significant.

Results

Recurrence occurred in 72 (41.1%) of 175 patients. Lymph node recurrence, organ metastasis, pleural dissemination, and a combination of these were observed in 39 (22.3%), 15 (8.6%), 4 (2.3%), and 14 (8.0%) patients, respectively (Table 1a). In total, 51 cases showed lymph node recurrence, 17 of which were found within the dissected area. The first choice of treatment for recurrence is also shown in Table 1a. Various kinds of treatment were indicated for each mode of recurrence, which clearly showed that there was no definite strategy for treatment of recurrence, depending on the extent of recurrent diseases, the presence or absence of pervious neoadjuvant and/or adjuvant treatments, and the patient's general status at the diagnosis of recurrence.

Forty (55.6%) and 22 (30.6%) of the 72 cases presented with recurrences in the first and second year after the initial operation, respectively, thus indicating that more than

Table 1. (b) Time to recurrence after a curative esophagectomy for cancer

Months after surgery	Number of cases	Cumulative ratio
Earlier than 6 months	20	
From 6 to 12 months	20	56%
From 12 to 18 months	13	
From 18 to 24 months	9	86%
Later than 24 months	10	100%
Total	72	100%

86% of recurrences occurred within 2 years after surgery (Table 1b). However, 4 of the remaining 10 cases presented their recurrences later than 4 years after the operation (data not shown).

The relationship between recurrence and clinicopathological features at surgery is shown in Table 2a. A univariate analysis showed statistically significant associations between recurrence and the pathological depth of tumor invasion (pT), pathological lymph node metastasis (pN), pathological stage (pStage), permeation to lymphatic vessels and venous invasion, the number of fields (cervical, mediastinal, or abdominal) where lymph node metastasis was observed, and the number of metastasized lymph nodes (0–4 vs. 5 and more: this way of division yielded the statistically largest difference). The average numbers of metastasized lymph nodes were 3.84 and 0.74 in the recurrent and nonrecurrent patients, respectively, which showed a statistically significant difference ($P < 0.0001$) (data not shown). A logistic regression analysis including these factors indicated that only the presence of permeation to lymphatic vessels ($P < 0.05$, odds ratio = 5.11, 95% confidence interval = 1.34–19.45) and lymph node metastasis when observed in more than two fields ($P < 0.001$, odds ratio = 4.78, 95% confidence interval = 1.99–11.47) were selected as statistically significant factors that would predict recurrence after surgery (Table 2b).

The surveillance tools that first indicated a suspicion of recurrence (first indicator, FI) were investigated. Table 3 shows that 39 (54.2%) of 72 patients with recurrence were suspected to have recurrence by a clinical visit including anamnesis of history (symptoms) and signs observed during a physical examination. Symptoms most frequently observed were pain at metastasized sites, general fatigue, dysphagia, and appetite loss. Signs most frequently observed were fever, cough and sputum caused by pneumonia, hoarseness,

Table 2. Relationship between recurrence and clinicopathological factors after a curative esophagectomy for esophageal cancer
(a) Univariate analysis

Variables	Recurrence (+) (n = 72)	Recurrence (–) (n = 103)	P value
Age (years)	61.8 ± 8.4	62.0 ± 7.8	N.S.
Gender (male/female)	64/8	84/19	N.S.
Tumor location:			
Upper/Middle/Lower	10/32/30	13/58/32	N.S.
Depth of tumor invasion			
pT 0, 1/2, 3	16/56	47/56	<0.0001
Lymph node metastasis			
pN 0, 1, 2/3, 4	31/41	76/25	<0.0001
Pathological stage			
pStage 0, I, II/III, IV	27/45	81/22	<0.0001
Lymph vessel permeation			
ly (–)/(+)	26/46	83/20	<0.0001
Vascular invasion			
v (–)/(+)	41/31	85/18	<0.0001
No. of fields of LNM			
0, 1/2, 3	40/32	94/9	<0.0001
No. of metastasized LN			
0–4/5 and more	54/18	99/4	<0.0001

pT, pN, pStage are according to references 11, 12
N.S., not significant; LN, lymph node; LNM, LN metastasis

(b) Multivariate analysis (logistic regression analysis)

Variables	P values	Odds ratio	95% CI
pT 0, 1/2, 3	0.16	1.87	(0.78–4.46)
pN 0, 1, 2/3, 4	0.35	0.54	(0.15–1.94)
pStage 0, I, II/III, IV	0.37	1.83	(0.49–6.88)
ly (–)/(+)	<0.05	5.11	(1.34–19.45)
v (–)/(+)	0.27	2.71	(0.46–15.91)
No. of fields of LNM			
0, 1/2, 3	<0.001	4.78	(1.99–11.47)
No. of metastasized LN			
0–4/5 and more	0.98	1.10	(0.39–2.63)

CI, confidence interval

Table 3. First indicators to suspect recurrence and its frequency

First indicator	No. of patients
Clinical visit	39 (54%)
Symptoms	36 (50%)
Signs	22 (31%)
Tumor marker	33 (46%)
CEA	9 (13%)
SCC-Ag	28 (39%)
Imaging	49 (68%)
CT	45 (63%)
US	8 (11%)
Imaging only[a]	19 (26%)

CEA, carcinoembryonic antigen; SCC-Ag, squamous cell carcinoma
[a]Imaging only means the cases in which imaging was exclusive first indicator without any other first indicators such as clinical visit or tumor marker

and abnormal neurological findings such as paralysis. The FI in 33 cases (45.8%) was monitoring of tumor markers of CEA and/or SCC-Ag. Imaging including CT and/or US indicated a suspected recurrence in 49 cases (68.1%). Imaging was the exclusive FI in 19 cases (i.e., no symptoms or signs, normal levels of tumor marker; 26.4%).

The FIs were compared between 40 patients within 12 months after surgery and 32 patients more than 12 months after surgery among the recurrent patients. The FIs of them were clinical visit (65.0% and 40.6%, P = 0.039), tumor marker abnormalities (55.0% and 34.4%, P = 0.081), and imaging (70.0% and 65.6%, P = 0.69), respectively. The rate of patients whose recurrences were found by exclusively imaging abnormalities without any symptoms, signs, or abnormal tumor marker levels was less frequent in the former group (17.5%) than in the latter one (37.5%), although this difference was statistically not significant (P = 0.056).

The overall survival rates were compared by the time to recurrence, mode of recurrence, and various FIs. The overall 1- and 3-year survival rates of all cases after the diagnosis of recurrence were 29% and 14%, and the median survival time (MST) was 7 months (data not shown). The MSTs of cases with lymph node recurrence, organ metastasis, and combined recurrence were 9, 6, and 6 months, respectively, showing no significant differences. There are 4 patients who are still alive 30 months after recurrence. The mode of recurrence, treatment modalities, and prognosis of each of these cases are solitary brain metastasis, gamma-knife radiotherapy, and 43 months (case 1); cervical lymph node metastasis, surgical resection, and 34 months (case 2); solitary lung metastasis, surgical resection, and 32 months (case

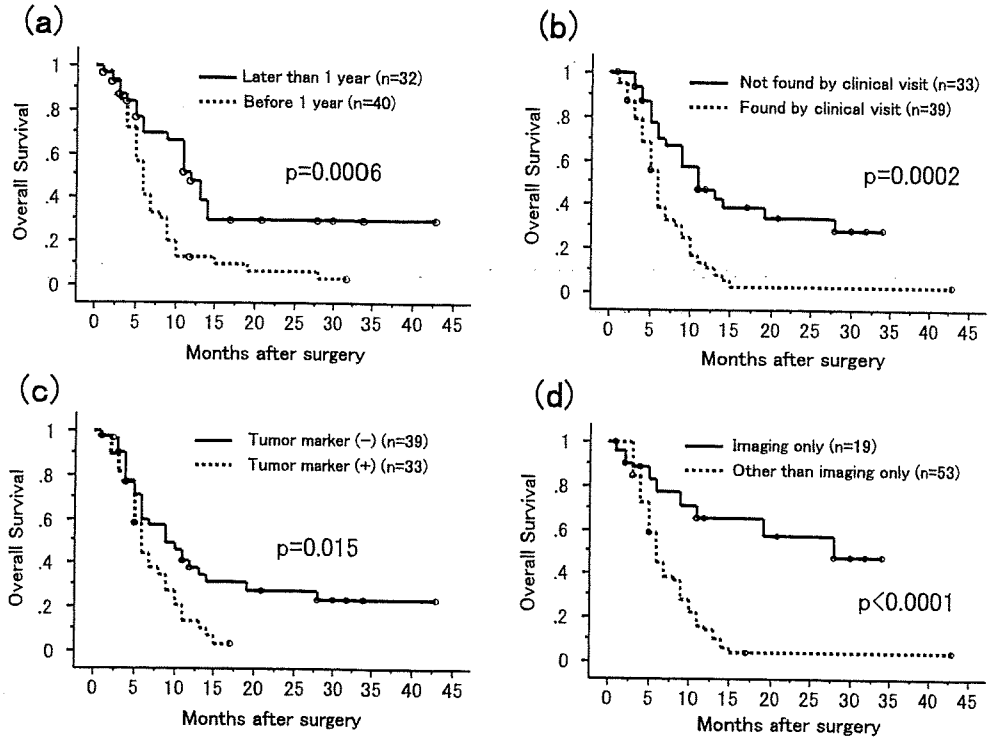

Fig. 2. Overall survival rates after recurrence of esophageal cancers were compared by time to recurrence [*later than 1 year* versus less than (*before*) *1 year* after surgery] (**a**), presence versus absence of symptoms and/or signs on *clinical visit* (**b**), presence versus absence of *tumor marker* abnormalities (**c**), and the cases in which *imaging* was the exclusive first indicator versus the cases that presented with any other first indicators (FIs) with or without imaging (**d**)

3); and lower mediastinal lymph node recurrence, chemoradiotherapy, and 30 months (case 4).

The patients whose recurrences were found later than 1 year after surgery showed significantly better survival rate than those within 1 year; 1- and 2-year survival rates were 47.3 % and 30.1%, respectively, in the former group and 12.8% and 6.4%, respectively, in the latter group (P = 0.0006) (Fig. 2a). When the recurrence was found by a clinical visit (symptom and/or signs), the prognosis was significantly worse than in those who showed no symptoms or signs (P = 0.0002; Fig. 2b). The patients who showed symptoms had a significantly poorer prognosis than those without (P = 0.0008). Similarly, the prognosis of the patients who showed any signs was significantly worse than those without signs (P = 0.036; data not shown). Abnormal serum tumor marker level (CEA and/or SCC-Ag) at the diagnosis of recurrence was also an unfavorable prognostic indicator (Fig. 2c). The prognosis of the patients whose FI was exclusively imaging (that is, patients who showed no symptom, sign, or abnormal tumor marker level) was significantly better than that of the patients who presented with any other FIs with or without imaging (P < 0.0001) (Fig. 2d).

The prognostic values of FIs for 40 patients who showed recurrences within 12 months after surgery were also analyzed. Importantly, the patients whose recurrences were found by exclusively imaging abnormalities without any symptoms, signs, or abnormal tumor marker levels (7 cases) showed a significantly longer survival rate than the remaining 33 cases (P = 0.0027 by log-rank test) (MST: 19.0 months vs. 6.0 months, P = 0.037 by a generalized Wilcoxon test).

Table 4 summarizes the results of a multivariate analysis to identify independent prognostic factors using a Cox's proportional hazards model. Subsequently, recurrences later than 1 year after surgery and when imaging was the exclusive FI were indicated to be independent factors for a favorable prognosis after recurrence (Table 4).

Discussion

The primary aim of the follow-up after a curative resection of an esophageal cancer is to detect local recurrence, distant metastasis, or metachronous primary cancers at an early stage when curative treatments are still possible, thus leading to an improvement of the prognosis. Follow-up is also important to evaluate and administrate the general condition and the quality of life of the patients, because an esophagectomy is associated with a significant level of surgical stress. However, achieving a successful cure of patients with recurrence is extremely rare even after multimodality therapies. The MST after a diagnosis of recurrence is about 5–8 months [2–4,8,9]. Nevertheless, it is also obvious that there are a few patients who could be cured if their recurrence were diagnosed at an early stage [13–15]. Furthermore, even when a curative treatment is impossible, early detection of recurrence could possibly provide patients with a better compliance for various treatments and with an opportunity to obtain a more prolonged survival and a better quality of life. The fact that patients whose FI was exclusively imaging (that is, patients who showed no symptoms, signs, or abnormal tumor marker levels) had a significantly longer survival rate clearly indicates the usefulness of a regular follow-up, and this is also true among the patients whose recurrences were found within 12 months after surgery. Thus, these data strongly suggest that the

Table 4. A Cox's proportional hazards model for factors predictive of prognosis after recurrence

Variables	*P* value	Hazards ratio	95% CI
Time of recurrence			
<1 year vs. >1 year	0.002	3.04	(1.51–6.12)
Symptoms (–) vs. (+)	0.27	2.08	(0.57–7.59)
Signs (–) vs. (+)	0.12	1.87	(0.85–4.10)
Clinical visit[a]			
(–) vs. (+)	0.28	0.39	(0.071–2.19)
Tumor marker[b]			
(–) vs. (+)	0.78	1.18	(0.36–3.86)
Imaging[c]			
(–) vs. (+)	0.30	0.49	(0.13–1.86)
Imaging only[d]			
(–) vs. (+)	0.011	5.22	(1.46–18.68)

CI, confidence interval
[a]Clinical visit: symptom and/or signs
[b]Tumor marker: CEA and/or SCC-Ag
[c]Imaging: CT and/or US
[d]Imaging only: the cases in which imaging was exclusive first indicator without any other first indicators such as clinical visit or tumor marker

patients whose recurrences could be found before appearance of any symptoms, signs, or tumor marker abnormalities can expect a better chance of longer survival.

No standard method for postoperative follow-up observation after a curative esophagectomy for esophageal cancer has been established. The clinical practice guidelines for esophageal cancer established by NCCN [6] state a brief follow-up: (1) for asymptomatic patients, complete history and physical examination every 4 months for 1 year, then every 6 months for 2 years, and annually thereafter, and (2) circulating blood cell count and serum chemistry evaluation, endoscopy, and imaging studies as clinically indicated. However, no evidence or references are cited in this guideline. The clinical recommendations for esophageal cancer by ESMO show no method for postoperative follow-up and note that there is no evidence that regular follow-up after initial therapy influences the outcome [7]. The Japanese guidelines [5] briefly discuss the follow-up procedures, including imaging modalities, to be used, but again no definite data or evidence is presented.

This report documented the follow-up method used in this institute. This method identified the FIs that suggested recurrence and the factors predictive of prognosis after recurrence. More than half (54%) of the recurrences were suspected merely by clinical visits (symptom and/or sign), indicating that complete anamnesis and the history and physical examination of the patient are extremely important on every clinical visit. Measurement of the serum level of tumor markers, including CEA and SCC-Ag, is also effective to find recurrences. In particular, the SCC-Ag level was increased in about 40% of the patients with recurrence. Imaging including CT and/or US was also shown to be effective for follow-up. CT and US were performed at the same time because the use of both these imaging methods sometimes complemented the deficiencies of the other. Four patients were suspected to have recurrence by only US but not by CT (data not shown).

These FIs could therefore be factors predictive of the prognosis after recurrence. A univariate analysis indicated the presence of symptoms and/or signs, and abnormal tumor maker levels at the diagnosis of recurrence would predict more unfavorable prognosis after recurrence. In contrast, the patients whose recurrences were identified by imaging only (i.e., no symptoms or signs, and normal level of tumor markers) could therefore expect a significantly better prognosis after recurrence. A multivariate analysis also demonstrated that this factor could be an independent predictor of a favorable prognosis. This finding clearly showed that recurrence should be found as early as possible before appearance of any symptoms, signs, or tumor marker abnormalities. Furthermore, patients with recurrence later than 1 year after the initial operation were shown to have significantly better prognosis than those before 1 year in both the univariate and multivariate analyses, which may mean that recurrent lesions found within a year after surgery consisted of tumor cells with more aggressive potential than those after 1 year. However, even in such cases, earlier detection of recurrence would give a greater possibility for cure by multimodality treatments including surgery and chemoradiotherapy. Considering that most recurrences occurred within 2 years after the operation, postoperative follow-up should be more intensive for the first 2 years and less intensive for the following 3 years.

Recently, FDG-PET has been shown to be effective in detecting recurrence of esophageal cancer after surgical resection. FDG-PET seems to be more accurate that conventional CT for detection of both locoregional recurrence and distant metastases, except small lung metastasis [16,17]. The fact that FDG-PET has a larger field of imaging than CT can be another merit for detecting recurrences. However, FDG-PET is not always facilitated in most hospitals, including this one, and is reserved for patients with suspected recurrence detected by the conventional follow-up system.

It is also mandatory to check for the development of either asynchronous remnant esophageal cancer or asynchronous multiple cancers of other organs such as of the stomach (gastric tube used for reconstruction) or head and neck region. Sato et al. reported that a second malignancy was the major cause of death among the patients without any lymph node metastasis who underwent an esophagectomy for thoracic esophageal cancer [18]. Therefore, endoscopic examinations are conducted for the head and neck region, remnant esophagus, stomach, and colorectum (see Fig. 1).

Conclusions

No standard follow-up method after a curative esophagectomy for esophageal cancer has yet been established. Furthermore, so far few studies have investigated the effectiveness of any follow-up schedules including the frequency and modalities used. The efficacy and suitability of the schedule shown in this article for the cure of patients with recurrence of esophageal cancer are not known. A nationwide accumulation of larger-scale clinical data based on a fixed schedule with a consensus is necessary to obtain evidence for the diagnosis and treatment of recurrent esophageal cancer. In the future, the performance of meta-analyses using the findings of many reports on postoperative follow-up are absolutely required.

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