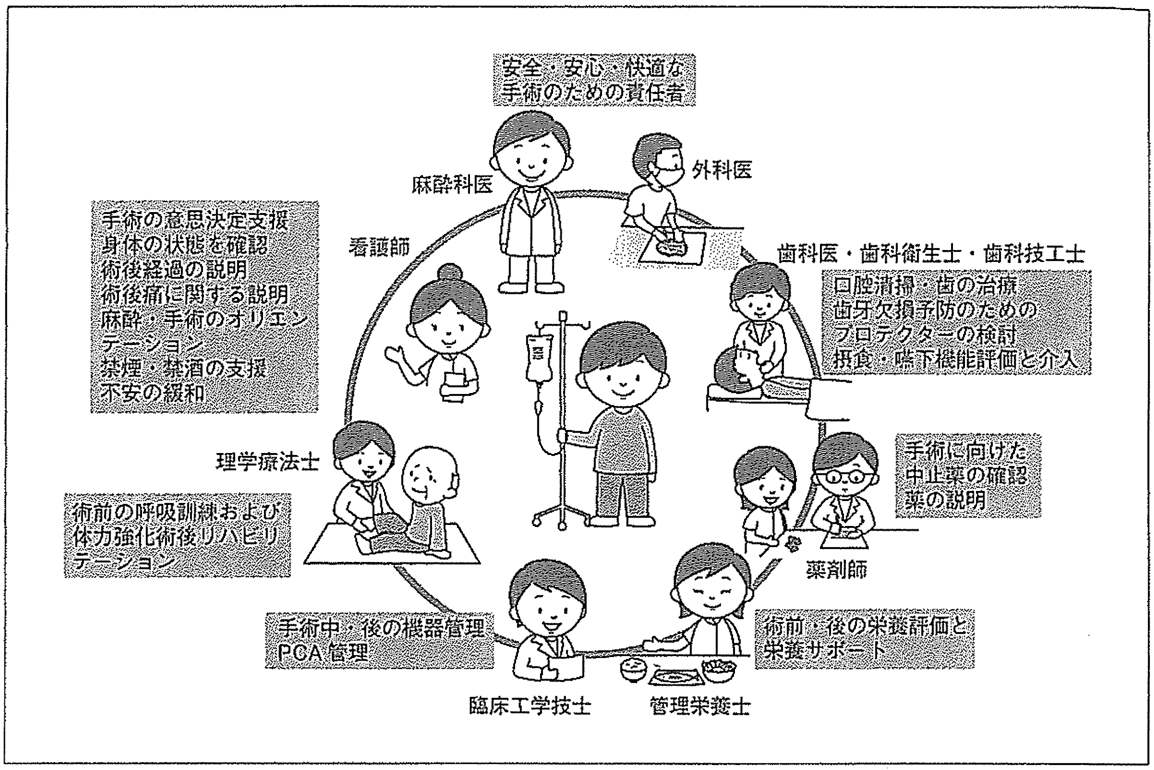

図1. PERIOのメンバーとその役割

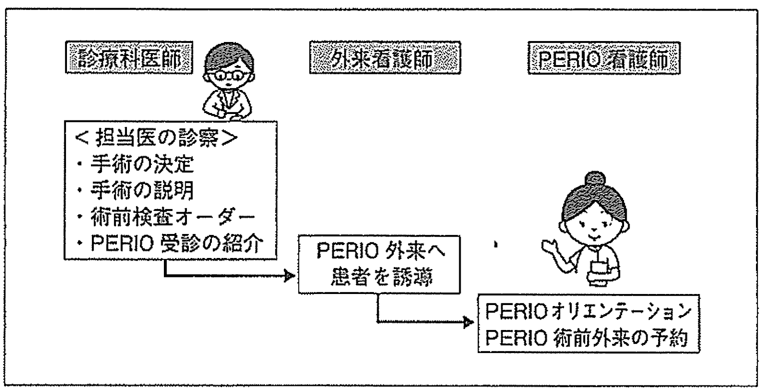

図2. 手術決定の外来日

腺・内分泌外科手術患者，脳外科手術患者にも対象を広げている．

Ⅱ. PERIOにおけるチーム医療

PERIOを構成するチームメンバーは外科医，麻酔科医，PERIO看護師，理学療法士，臨床工学技士，管理栄養士，薬剤師，歯科医，歯科衛生士，歯科技工士からなっており，各メンバーの役割は図1に示すとおりである．

PERIOの最大の特徴は，外来時点から介入が開始されることである．食道癌患者を例にとると，患者が外科を受診し検査後，手術が決定した時点でPERIOへ紹介となる．続いてPERIO看護師がオリエンテーションを行い，初回の外来を予約する(図2)．PERIO外来では約4時間をかけ，PERIO看護師，理学療法士，薬剤師，歯科部門，管理栄

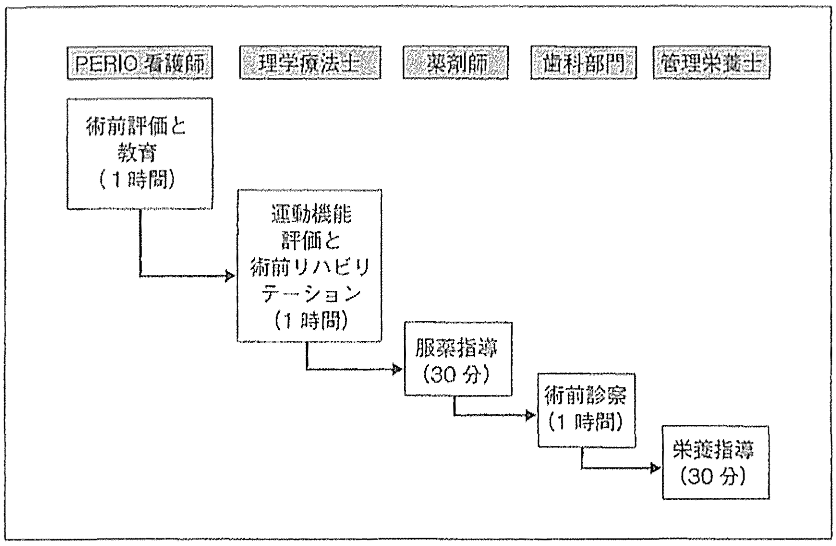

図3．PERIO外来日
受診時間は約4時間である．

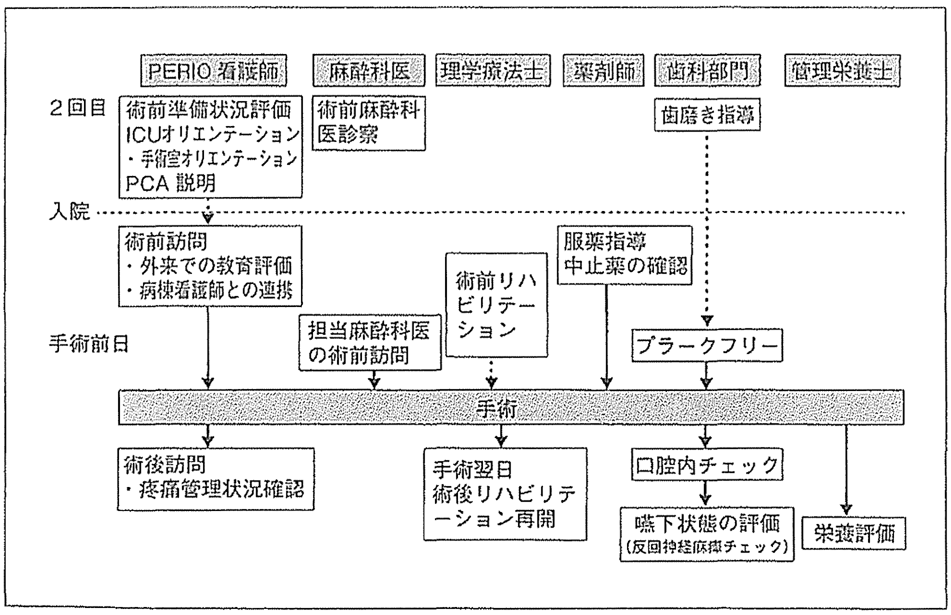

図4．PERIO外来2回目と入院後
ICU：集中治療室，PCA：自己調節鎮痛法

養士による評価と介入が行われる（図3）．さらに食道癌患者では，入院前にもう一度PERIO外来を受診して，PERIO看護師による準備状況の再評価，術前麻酔科医診察，歯科部門の口腔ケアなどが行われる．入院（通常手術の2日前）後も手術の前後で図4に示す介入が行われている．

なおPERIOの介入業務は，すべて担当医による紹介状や依頼状を介することなく自動的に遂行できる体制となっており，外科医の負担軽減に大きく役立っている．また，PERIOのチームメンバー間の情報交換も重要と考えている．当院では電子カルテ内に周術期管理センターカルテを作成

し，メンバーは自由に閲覧できるようにして組織横断的な情報共有に役立てている．

PERIO導入の成果としては，食道癌手術患者において，術後の歩行開始までの日数が5日から3日（鏡視下例は1日），術後在院日数が49日から24日（鏡視下例は16日）〔いずれも中央値〕と有意に短縮したが，これは術後肺炎発生率の低下が大きな要因であった．

また，PERIOでもERASプロトコルの大部分を取り入れている．そこで，その実際を学ぶためにERAS Societyの教育施設Centers of Excellenceでの研修を多職種チームで行ってきた（図5）．2012年はスウェーデンÖrebro University Hospital（Olle Ljungqvist教授），2013年はカナダMcGill University Health Center（Francesco Carli教授）を訪問した．

図5．ERAS Societyの教育施設視察
2012年，外科医，麻酔科医，歯科医，看護師，薬剤師，管理栄養士，理学療法士のチームでERAS SocietyのChairmanであるOlle Ljungqvist教授がおられるÖrebro University Hospitalを訪問した．

Ⅲ．ERASにおけるチーム医療

ERASにおいてもチーム医療は必須であり，われわれが訪れた二つの先進施設でもプロトコルの実践のため多職種の介入が行われていた．外科医による鏡視下手術導入などの工夫，麻酔科医による術中・術後の疼痛および輸液管理と嘔気・嘔吐予防，管理栄養士による術前・術後の絶食期間を短縮するための栄養管理，看護師による入院前カウンセリング，理学療法士による術前理学療法と早期離床推進などが行われていた．

特に興味深いものとしては，McGill University Health Centerにおける看護師による徹底した術前教育があげられる．ヘルス・リテラシー（健康面での適切な意思決定に必要な基本的健康情報やサービスを調べ，得，理解し，効果的に利用する個人的能力の程度）が低い患者は，さまざまな問題が発生するため術後の予後もわるいとされており，その改善のための手法として「teach back method」などを取り入れた患者教育の工夫がなされていた．また患者教育用のWebサイト[10]も非常に充実していた．さらにメディカルスタッフ以外のチームメンバーの参画も興味深かった．ERAS SocietyにはERAS interactive audit system（EIAS）という優れたデータベースがあるが，これを管理するデータマネージャーや，周術期管理に関するエビデンスとなるようなさまざまな文献などの情報をチームに提供する，本邦では珍しいclinical librarianなどをメンバーに擁していた．彼らの業務もERAS Study Groupが常に新しいエビデンスを発信し続けている原動力の一つのように感じられた．

Ⅳ．ERASとPERIOの比較

ERASは術後回復強化をめざして比較的低侵襲な大腸癌手術からスタートしているのに対して，PERIOは合併症発生抑制をめざして比較的高侵襲な呼吸器外科手術や食道癌手術からスタートした．結果的にPERIOにおける業務内容の多くはERASプロトコルに準じたかたちとなっている．しかしながら，PERIOにはERASには含まれない歯科部門がチームメンバーに含まれていることは大きな特徴である．

近年，術後呼吸器合併症の予防のための口腔ケアの重要性が注目されている[11～13]．さらに食道癌や頭頸部癌の術後においては，嚥下機能評価および摂食・嚥下リハビリテーションは，患者の術後quality of life（QOL）の向上のために重要である[14,15]．ERAS Societyからは大腸癌以外の手術に対するガイドラインも近年発表されているが[3～9]，それぞれの疾患でのプロトコルはエビデンスレベルに基づきバリエーションが認められている．よって，食道癌手術に対するガイドラインが発表される際には，歯科部門の介入も盛り込まれるこ

とも期待したい．

おわりに

ERASプロトコルはすでに合併症減少や在院日数短縮などのエビデンスが知られており[16,17]，導入は比較的容易である．しかし，わが国の保険制度や急速に高齢化がすすんでいる社会情勢を鑑みた対応は必要であろう．その際，プロトコルを部分的に取り入れ，独自の工夫を加えた当院のPERIOのようなチーム医療は有用かもしれない．しかし，その成果をより高めるためには，それぞれのメンバーの組織内における「コンピテンシー」を明確化し，その能力を獲得できるシステム作りが重要となるであろう．

◆◆◆ 文献 ◆◆◆

1) Fearon KC, Ljungqvist O, Von Meyenfeldt M et al : Enhanced recovery after surgery ; a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 24 : 466-477, 2005
2) Lassen K, Soop M, Nygren J et al : Consensus review of optimal perioperative care in colorectal surgery ; Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 144 : 961-969, 2009
3) Gustafsson UO, Scott MJ, Schwenk W et al : Guidelines for perioperative care in elective colonic surgery : Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 31 : 783-800, 2012
4) Nygren J, Thacker J, Carli F et al : Guidelines for perioperative care in elective rectal/pelvic surgery : Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 31 : 801-816, 2012
5) Nygren J, Thacker J, Carli F et al : Guidelines for perioperative care in elective rectal/pelvic surgery ; Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg 37 : 285-305, 2013
6) Lassen K, Coolsen MM, Slim K et al : Guidelines for perioperative care for pancreaticoduodenectomy ; Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 31 : 817-830, 2012
7) Lassen K, Coolsen MM, Slim K et al : Guidelines for perioperative care for pancreaticoduodenectomy ; Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg 37 : 240-258, 2013
8) Cerantola Y, Valerio M, Persson B et al : Guidelines for perioperative care after radical cystectomy for bladder cancer : Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 32 : 879-887, 2013
9) Mortensen K, Nilsson M, Slim K et al : Consensus guidelines for enhanced recovery after gastrectomy : Enhanced Recovery After Surgery (ERAS) Society recommendations. Br J Surg 101 : 1209-1229, 2014
10) MUHC Patient Education 1. < http : //www.muhcpatienteducation.ca/?q=home-page > [Accessed 2014 Dec 23]
11) Akutsu Y, Matsubara H : Perioperative management for the prevention of postoperative pneumonia with esophageal surgery. Ann Thorac Cardiovasc Surg 15 : 280-285, 2009
12) Akutsu Y, Matsubara H, Shuto K et al : Preoperative dental brushing can reduce the risk of postoperative pneumonia in esophageal cancer patients. Surgery 147 : 497-502, 2010
13) 足立忠文，三木仁美，松澤恵梨子ほか：食道癌周術期における術後肺炎に対する口腔ケアの効用について．日摂食嚥下リハ会誌12：40-48，2008
14) 坪佐恭宏，佐藤　弘，根本昌之ほか：胸部食道癌根治術後の嚥下障害に対する摂食嚥下リハビリテーションの施行経験．日消外会誌38：571-576，2005
15) 舘村　卓，佐々生康宏：専門的口腔ケアと全身とのかかわり―医歯連携医療―食道癌手術患者への口腔ケアを通じた摂食嚥下リハビリテーション（歯科医科連携の観点から）．歯臨研4：40-48，2007
16) Ljungqvist O : ERAS ; enhanced recovery after surgery. J Visc Surg 148 : 157-159, 2011
17) Ljungqvist O : ERAS ; enhanced recovery after surgery ; moving evidence-based perioperative care to Practice. JPEN J Parenter Enteral Nutr 38 : 559-566, 2014

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Changes in Body Composition Secondary to Neoadjuvant Chemotherapy for Advanced Esophageal Cancer are Related to the Occurrence of Postoperative Complications After Esophagectomy

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ABSTRACT

Background. Although a survival benefit of neoadjuvant treatment for patients with esophageal cancer has been highlighted, the influence of neoadjuvant treatment on the nutritional status of patients with esophageal cancer is not well understood.

Methods. Changes in body composition parameters were assessed in 30 patients who underwent neoadjuvant chemotherapy (NAC) comprising docetaxel, cisplatin, and 5-fluorouracil followed by esophagectomy from August 2009 to April 2013. Body composition was evaluated before and after NAC using multifrequency bioelectrical impedance analysis (InBody 720; Biospace, Tokyo, Japan). Postoperative complications were graded according to the Clavien-Dindo classification.

Results. Twenty-three postoperative events occurred in 16 patients. A decrease in body protein was observed in 13 patients (43.3 %), while skeletal muscle (SM), body cell mass (BCM), and fat-free mass (FFM) declined in 11 patients (36.7 %) during NAC. Changes in these four parameters during chemotherapy significantly differed between patients with postoperative complications and those without: protein, -1.6 ± 0.9 versus $+4.4 \pm 2.1$ kg ($P = 0.01$); SM, -1.3 ± 1.1 versus $+4.7 \pm 2.4$ kg ($P = 0.02$); BCM, -2.4 ± 1.6 versus $+3.8 \pm 2.2$ kg ($P = 0.03$); and FFM, -1.4 ± 1.4 versus $+4.3 \pm 2.3$ kg ($P = 0.04$).

Conclusions. Changes in body composition parameters are possible predictive markers of postoperative complications after esophagectomy after NAC. Further analysis is needed to clarify whether nutritional intervention improves such parameters and thus contributes to reduced postoperative morbidity.

Esophagectomy for esophageal cancer is associated with high morbidity and mortality rates.[1,2] Moreover, it has been established that preoperative treatment, which has substantial toxicity, should be performed for patients with resectable advanced esophageal cancer.[3] In Japan, preoperative chemotherapy using cisplatin plus 5-fluorouracil (CF) is the current standard treatment for clinical stage II/III squamous cell carcinoma based on the results of the JCOG 9907 trial.[4] An additional study of this trial revealed that preoperative CF did not increase the incidence of postoperative complications compared with surgery without preoperative treatment.[5]

Docetaxel combined with CF (DCF), which has strong antitumor activity against esophageal squamous cell carcinoma, is considered to be the next candidate for a standard neoadjuvant chemotherapy (NAC) regimen.[6] However, this regimen has relatively high toxicity; thus, there is concern over a potential increase in perioperative complications. We previously reported that preoperative DCF did not negatively affect subsequent esophagectomy with regard to the frequency of complications. In that

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study, however, we also observed significant decreases in serum albumin (Alb) levels among patients who underwent two courses of DCF.[7] This result indicates that preoperative DCF may negatively affect the nutritional status of patients with esophageal cancer.

Bioelectrical impedance analysis is a safe and noninvasive method for evaluating body composition.[8,9] Recent reports suggested that measurement of body composition is useful for the evaluation of the nutritional status of surgical patients and prediction of prognosis.[10] However, few reports have demonstrated changes in the body composition during NAC for esophageal cancer. In addition, the correlation between changes in the body composition and the risk of postoperative complications has not been clarified.

The aim of this study was to determine the influence of neoadjuvant DCF on the body composition of patients with esophageal cancer and to evaluate whether body composition changes affect the incidence of postoperative complications.

MATERIALS AND METHODS

Patients

Fifty-two patients with esophageal squamous cell carcinoma underwent esophagectomy after NAC from August 2010 to April 2013 at the Department of Gastroenterological Surgery, Kumamoto University Hospital. Thirteen patients who could not undergo body composition analysis, four who underwent NAC with a regimen other than DCF, three with simultaneous double primary cancer, one who underwent transhiatal esophagectomy, and one who underwent a two-stage operation were excluded from this study. The remaining 30 patients were eligible. There were 25 male and 5 female patients with a mean age of 64.0 years (range 53–75 years). This study was approved by the institutional review board of Kumamoto University Hospital.

Tumor staging was based on the tumor, node, metastasis system classification defined by the Union for International Cancer Control.[11] The pretreatment diagnostic evaluations comprised a barium swallow, endoscopy, computed tomography, and ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography.

NAC

Patients with resectable esophageal cancer with lymph node metastasis were treated with NAC followed by esophagectomy. The NAC regimen comprised 60 mg/m^2 of docetaxel provided intravenously on day 1, 350 mg/m^2 of 5-fluorouracil provided as a 24-h continuous intravenous infusion on days 1–5, and 6 mg/m^2 of cisplatin provided intravenously on days 1 to 5.[6]

TABLE 1 Patient characteristics

Characteristic	Value
Age, year, mean (range)	65 (53–75)
Sex (M/F)	25/5
Location of main tumor (Ut/Mt/Lt)	2/23/5
cT factor (1b/2/3/4)	3/5/22/0
cN factor (0/1/2/3/4)	0/11/12/7/0
cStage (IB/IIA/IIB/IIIA/IIIB/IIIC/IV)	1/0/4/12/11/1/1

Ut upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic esophagus

Nutritional Assessment

The body composition was assessed before and after NAC using multifrequency bioelectrical impedance with eight tactile electrodes (InBody 720; Biospace, Tokyo, Japan). Various parameters, including body weight, body mass index (BMI), protein, fat mass, total body water, mineral content, skeletal muscle (SM), body cell mass (BCM), and fat-free mass (FFM), were automatically measured. We also collected data from blood tests, including serum total protein (TP) and Alb, from the patients' records.

Outcome Evaluation

Postoperative complications were defined according to the Clavien-Dindo classification.[12]

Statistical Analysis

Data are expressed as mean ± standard error. Statistical analyses were performed by StatView software (SAS Institute, Cary, NC, USA). When appropriate, data were submitted to statistical analysis using the Mann-Whitney *U* test or Student's *t* test. A *P* value of <0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of the patients are summarized in Table 1. The primary tumor was located in the upper, middle, and lower thoracic esophagus in 2, 23, and 5 patients, respectively. One patient had stage IB cancer, and the 29 remaining patients had stage IIB to IV cancer. Twenty-eight patients completed two courses of planned chemotherapy, while the remaining two patients underwent only one course. After the NAC, subtotal esophagectomy

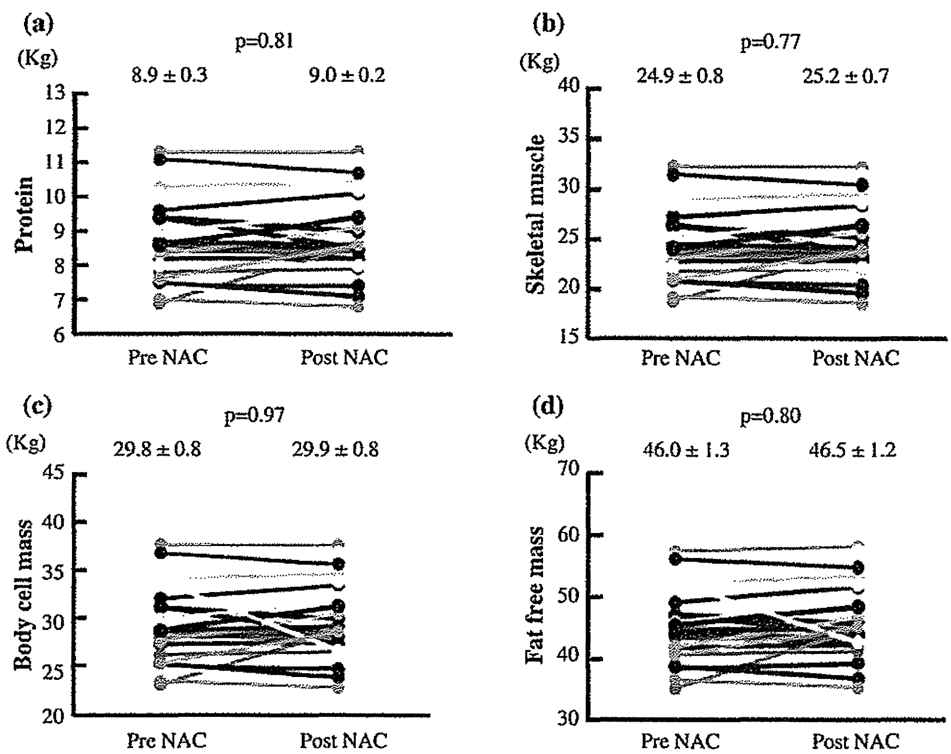


FIG. 1 Changes in nutritional parameters during NAC of **a** protein, **b** skeletal muscle, **c** body cell mass, and **d** fat-free mass

was performed for all 30 patients. A gastric tube was used for reconstruction in 29 patients, while a left colon graft was used for 1 patient. Reconstruction via the retrosternal route, intrathoracic route, and subcutaneous route was performed in 26, 2, and 2 patients, respectively. Cervical anastomosis was performed in all patients. The mean operative duration and blood loss were 550.0 ± 19.5 min (median 538.0 min; range 398.0–961.0 min) and 787 ± 268 ml (median 455 ml; range 138–8375 ml), respectively.

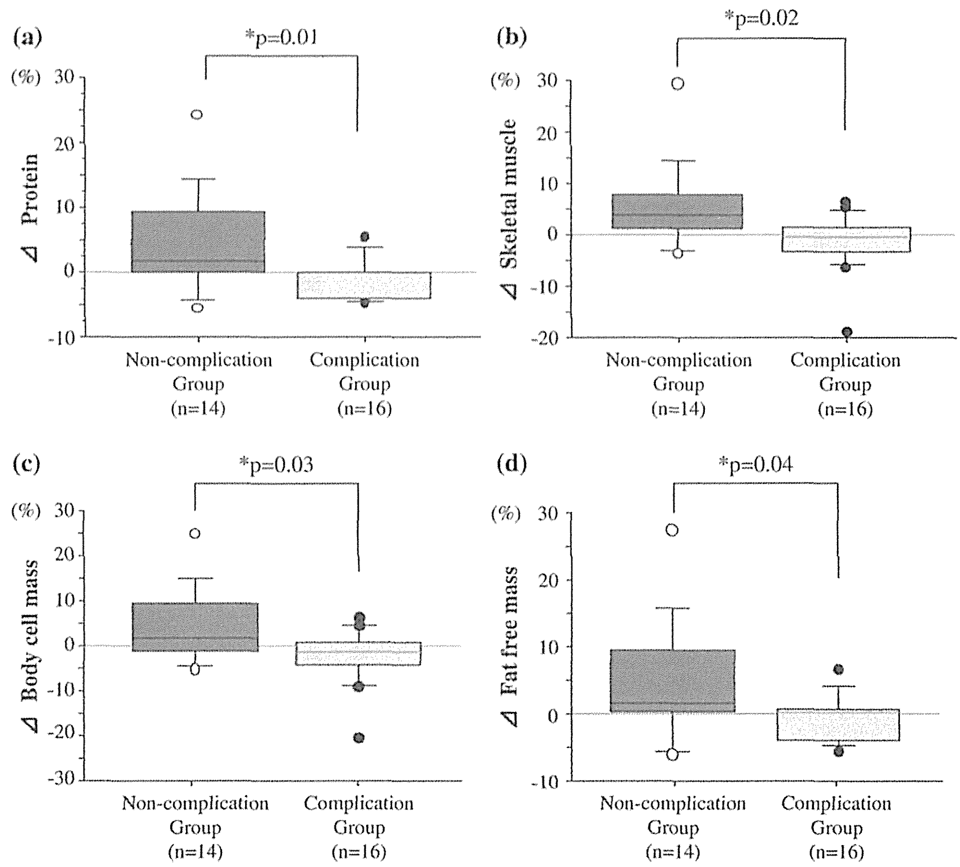
No statistical change in body weight or BMI was observed as a result of chemotherapy (Supplementary Fig. 1a, b). NAC did not affect the parameters of the In-Body 720, including protein, fat mass, total body water, mineral content, SM, BCM, or FFM (Fig. 1a–d) (Supplementary Fig. 1c–e). In addition, there was no relationship between the change of body composition and the effect of NAC.

Overall, 23 postoperative events occurred in 16 patients (53.3 %). Respiratory complications, surgical site infection, anastomotic leakage, and other complications developed in six, six, three, and eight patients, respectively. There was no relation between the nutritional parameters before NAC and occurrence of the postoperative complications. Changes in body weight and BMI were comparable between patients who did and did not develop postoperative complications. A decrease in protein secondary to NAC was observed in 13 (43.3 %) of 30 patients, while SM, BCM, and FFM declined in 11 patients (36.7 %). The mean change in protein (Δprotein) in patients with and without complications was −1.6 ± 0.9 and +4.4 ± 2.1 kg, respectively ($P = 0.01$). Similarly, ΔSM, ΔBCM, and ΔFFM were significantly different between patients with and without complications: ΔSM, −1.3 ± 1.1 versus +4.7 ± 2.4 kg ($P = 0.02$); ΔBCM, −2.4 ± 1.6 versus +3.8 ± 2.2 kg ($P = 0.03$); and ΔFFM, −1.4 ± 1.4 versus +4.3 ± 2.3 kg ($P = 0.04$) (Fig. 2). The mean change in other parameters, such as body weight and BMI, were not significantly different with complications (Supplementary Fig. 2). Changes in the levels of serum Alb and TP did not affect the occurrence of the postoperative complications. In addition, no significant difference was observed in the change of the value of serum TP and Alb between patients with and without complications: ΔTP, −10.9 ± 2.6 versus −8.6 ± 2.0 g/dl ($P = 0.50$); ΔAlb, −9.2 ± 2.7 versus −8.7 ± 3.6 g/dl ($P = 0.92$). Furthermore, the mean changes in the value of serum Alb and body composition were not correlated (data not shown).

DISCUSSION

In this study, we clarified that changes in some body composition parameters induced by NAC differed between patients who developed postoperative complications after esophagectomy and those who did not. These results indicate that changes in a patient's nutritional status

FIG. 2 Correlation between body composition changes and the occurrence of postoperative complications for changes in a protein, b skeletal muscle, c body cell mass, and d fat-free mass



resulting from NAC may affect the occurrence of morbidity after esophagectomy.

Patients with esophageal cancer frequently develop dysphagia, leading to reduced food intake at the initial diagnosis. In addition, malnutrition is associated with an increased risk for postoperative complications in patients who have undergone esophagectomy.[13,14] Several recent studies have reported that intensive perioperative nutritional support was effective for the reduction of postoperative morbidity and mortality after esophagectomy. Ryan et al.[15] conducted a randomized controlled trial and found that enteral nutrition enriched with eicosapentaenoic acid preserved lean body mass after esophagectomy and prevented the occurrence of systemic inflammatory response syndrome.

Chemotherapy is associated with a variety of toxicities. Weight loss is often observed as a result of chemotherapy-induced anorexia. Previous studies reported that weight loss during chemotherapy was associated with decreased survival in some patients with cancer.[16,17] However, the influence of NAC on postoperative morbidity and mortality after esophagectomy has been unclear. Therefore, we performed a prospective analysis of patients' detailed nutritional status before and after NAC and investigated the correlation between changes in nutritional parameters and the occurrence of postoperative complications after esophagectomy.

The available methods of nutritional assessment involve anthropometric measurement and biochemical marker evaluation. Dual-energy X-ray absorptiometry is an accepted method for the estimation of whole-body and segmental body fat and FFM.[18,19] However, this technique has disadvantages in the clinical setting, such as the risk of radiation exposure and the high cost of the equipment. The serum protein most commonly used for nutritional assessment is Alb. Preoperative hypoalbuminemia is a well-known risk factor for surgical mortality.[20] However, the half-life of Alb is 20 days, and it is difficult to use it as an accurate nutritional index during NAC. Another biochemical parameter is the prognostic nutritional index. Previous studies showed that the preoperative prognostic nutritional index was significantly lower in patients who developed postoperative complications after esophagectomy.[14,17] However, this index reportedly has a low predictive value.[17]

For clinical use, bioelectrical impedance analysis is a safe, noninvasive, and rapid and can be performed repeatedly for evaluation of the body composition.[8,9] Among all body composition parameters, BCM and FFM have been regarded as the most meaningful for the assessment of malnutrition.[21] BCM is the sum of the intracellular fluid and protein and is a reliable parameter of the nutritional status. In addition, FFM comprises the nonfat components (SM, bone, and water) of the human body and is another known parameter of nutritional status. Previously, we reported that NAC did not influence the occurrence of postoperative complications, although the serum Alb value decreased by NAC.[7] In the current study, no significant difference was observed in the value of ΔAlb between patients with and without complications. The nutritional evaluation using body composition may be a useful parameter to predict the occurrence of postoperative complications after NAC.

In the current study, not only BCM and FFM but also protein and SM were significantly decreased in patients who developed postoperative complications. SM depletion, referred to as sarcopenia, predicts morbidity and mortality in patients undergoing digestive surgery.[10,22] Preoperative low protein and sarcopenia may be associated with nutrient deprivation resulting from postoperative catabolization of body protein. Furthermore, there is a possibility that these changes contribute to the onset of postoperative complications.

Limitations of the present study include the small number of cases and the single-institution design. A large-scale, multicenter study is needed for validation. Another limitation is that the nutritional management during NAC differed among the patients. Further studies are needed to clarify whether nutritional intervention during NAC improves these nutritional parameters and thus contributes to reduced postoperative complications. We previously reported that preoperative DCF did not negatively affect subsequent esophagectomy with regard to the frequency of complications. In that study, however, we also observed significant decreases in serum Alb levels among patients who underwent two courses of DCF.[7]

In conclusion, changes in some body component parameters during NAC were correlated with the occurrence of postoperative complications after esophagectomy. Further analysis is needed to clarify whether nutritional intervention during NAC improves these parameters and thus reduces postoperative complications.

DISCLOSURES The authors report no financial interests or potential conflicts of interest.

REFERENCES

1. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Br J Surg.* 1980;67:381–90.
2. Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. *Lancet Oncol.* 2003;4:481–8.
3. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol.* 2011;12:681–92.
4. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol.* 2012;19:68–74.
5. Hirao M, Ando N, Tsujinaka T, et al. Influence of preoperative chemotherapy for advanced thoracic oesophageal squamous cell carcinoma on perioperative complications. *Br J Surg.* 2011;98:1735–41.
6. Watanabe M, Nagai Y, Kinoshita K, et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil for patients with node-positive esophageal cancer. *Digestion.* 2011;83:146–52.
7. Yoshida N, Watanabe M, Baba Y, et al. Influence of preoperative docetaxel, cisplatin, and 5-fluorouracil on the incidence of complications after esophagectomy for resectable advanced esophageal cancer. *Dis Esophagus.* 2014;27:374–9.
8. Jaffrin MY, Morel H. Body fluid volumes measurements by impedance: a review of bioimpedance spectroscopy (BIS) and bioimpedance analysis (BIA) methods. *Med Eng Phys.* 2008;30:1257–69.
9. Kim M, Kim H. Accuracy of segmental multi-frequency bioelectrical impedance analysis for assessing whole-body and appendicular fat mass and lean soft tissue mass in frail women aged 75 years and older. *Eur J Clin Nutr.* 2013;67:395–400.
10. Kaido T, Mori A, Ogura Y, et al. Pre- and perioperative factors affecting infection after living donor liver transplantation. *Nutrition.* 2012;28:1104–8.
11. Sobin LH, Gospodarowicz MK, Wittekind CW. TNM classification of malignant tumours. 7th ed. New York: Wiley-Blackwell; 2009.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–13.
13. Grotenhuis BA, Wijnhoven BP, Grune F, van Bommel J, Tilanus HW, van Lanschot JJ. Preoperative risk assessment and prevention of complications in patients with esophageal cancer. *J Surg Oncol.* 2010;101:270–8.
14. Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D, Sugimachi K. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol.* 2002;28:396–400.
15. Ryan AM, Reynolds JV, Healy L, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg.* 2009;249:355–63.
16. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med.* 1980;69:491–7.
17. Han-Geurts IJ, Hop WC, Tran TC, Tilanus HW. Nutritional status as a risk factor in esophageal surgery. *Dig Surg.* 2006;23:159–63.
18. Chen Z, Wang Z, Lohman T, et al. Dual-energy X-ray absorptiometry is a valid tool for assessing skeletal muscle mass in older women. *J Nutr.* 2007;137:2775–80.
19. Jackson W, Alexander N, Schipper M, Fig L, Feng F, Jolly S. Characterization of changes in total body composition for patients with head and neck cancer undergoing chemoradiotherapy using dual-energy X-ray absorptiometry (DEXA). *Head Neck.* 2013. doi:10.1002/hed.23461.
20. Hennessey DB, Burke JP, Ni-Dhonochu T, Shields C, Winter DC, Mealy K. Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery: a multi-institutional study. *Ann Surg.* 2010;252:325–9.
21. Kawaguchi T, Taniguchi E, Itou M, et al. Body cell mass is a useful parameter for assessing malnutrition and severity of disease in non-ascitic cirrhotic patients with hepatocellular carcinoma or esophageal varices. *Int J Mol Med.* 2008;22:589–94.
22. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxford).* 2011;13:439–46.

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Outcomes of Preoperative Chemotherapy with Docetaxel, Cisplatin, and 5-Fluorouracil Followed by Esophagectomy in Patients with Resectable Node-Positive Esophageal Cancer

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ABSTRACT

Background. There is a consensus that neoadjuvant therapy is an essential component of treatment for resectable advanced esophageal cancer. The aim of this study was to evaluate the efficacy of preoperative docetaxel/cisplatin/5-fluorouracil (DCF) followed by esophagectomy for patients with node-positive esophageal cancer using a prospective database.

Methods. Fifty-five consecutive patients with resectable node-positive esophageal cancer were treated with preoperative DCF between August 2008 and December 2010. Of these patients, 54 completed 2 courses of DCF, and 50 underwent esophagectomy after the planned chemotherapy. Clinical and pathologic responses to DCF were investigated, as was patient prognosis. Cox proportional hazard regression was used to determine factors that independently affected recurrence.

Results. Complete response, partial response, stable disease, and progressive disease were observed in 5, 24, 24, and 2 patients, respectively. Overall, the clinical response rate was 53 %. Pathologic complete response was achieved in 6 cases (12 %), and the overall pathologic response rate was 36 %. Downstaging was observed in 23 cases (46 %). Two-year overall and disease-free survival rates were 78 and 56 %, respectively. Multivariate analysis revealed that residual tumor [R1/2; hazard ratio (HR) 5.21, 95 % confidence interval (CI) 1.64–17.2], pathologic poor response (grade 1a; HR 3.08, 95 % CI 1.08–11.1), and ypN (M1Lym; HR 13.3, 95 % CI 2.06–116) were independent predictors of recurrence.

Conclusions. DCF has strong antitumor activity for esophageal cancer and may confer survival benefits when used as preoperative chemotherapy.

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Esophagectomy remains the mainstay of treatment for esophageal cancer. However, the survival of patients treated with surgery alone is unfavorable, with median survival times ranging from 13.3 to 24.0 months.[1–6] Consequently, multidisciplinary approaches have been investigated with the goal of improving long-term outcomes. The results of a recent meta-analysis suggest that neoadjuvant therapy followed by surgery is associated with better survival than surgery alone.[7, 8]

The Japan Clinical Oncology Group (JCOG) 9204 study demonstrated that postoperative chemotherapy with cisplatin plus 5-fluorouracil (CF) improves the disease-free survival (DFS) of patients with node-positive stage II/III squamous cell carcinoma (SCC).[9] Thereafter, the JCOG 9907 study revealed that preoperative chemotherapy with CF was superior to postoperative chemotherapy in clinical stage II/III SCC.[10] Accordingly, the current standard treatment for resectable advanced esophageal cancer in Japan is neoadjuvant chemotherapy followed by surgery.

Although CF is the standard chemotherapeutic regimen for esophageal cancer, this regimen may not be powerful enough to substantially improve outcomes. Response rates associated with CF regimens for esophageal cancer are less than 40 %.[11, 12] In a subgroup analysis of JCOG 9907, no survival benefit was evident for patients with T3 tumors or clinical stage III diseases.[10] Recently, triplet chemotherapy using docetaxel in combination with CF (DCF) has been reported to have strong antitumor activity for esophageal cancer.[13] Therefore, it is considered a candidate for the next standard regimen of neoadjuvant chemotherapy. However, the survival benefit of preoperative DCF followed by esophagectomy remains unclear.

In this study, we investigated the outcomes of patients who underwent esophagectomy after preoperative DCF for node-positive esophageal cancer.

PATIENTS AND METHODS

Prospective Database for Preoperative DCF

Since August 2008, we have prospectively enrolled patients with resectable node-positive esophageal cancer for preoperative DCF followed by surgery. The eligibility criteria included the following: pathologically defined esophageal cancer without invasion of neighboring structures; lymph node metastasis diagnosed by ^{18}F-deoxyglucose positron emission tomography–computed tomography (FDG-PET/CT); no distant metastasis; no prior treatment; an Eastern Cooperative Oncology Group performance status of 0 to 2; an age of 20–80 years; and adequate bone marrow, renal, and hepatic function (absolute neutrophil count $>1.5 \times 10^9$/L and platelet count $>5.0 \times 10^9$/L; serum creatinine level <1.5 mg/dL; aspartate aminotransferase and alanine aminotransferase levels $<2\times$ the upper limits of normal; total bilirubin $<1.5\times$ the upper limit of normal). All patients provided written informed consent for their participation in this study. The local ethics committee of Kumamoto University approved this study.

Regimen of Preoperative DCF

The DCF regimen consisted of 60 mg/m^2 of docetaxel on day 1, administered intravenously for 2 h; 350 mg/m^2 of CF on days 1 to 5 as a 24 h continuous intravenous infusion; and 6 mg/m^2 of cisplatin on days 1–5, administered intravenously for 1 h.[13] We used a reduced dose regimen to minimize toxicity. Although there was no phase 1 study for this regimen, the efficacy and safety of this split-dose regimen as a second-line chemotherapy has been reported.[14] In addition, efficacy and toxicity of low-dose cisplatin and 5-fluorouracil for patients with SCC of the esophagus has been demonstrated in a phase 2 trial.[15] This regimen was administered every 3 weeks, and 2 scheduled courses were administered before esophagectomy.

Study Populations

From August 2008 through December 2010, a total of 55 patients met the eligibility criteria (intention-to-treat [ITT] population). One patient underwent esophagectomy after 1 course of DCF as a result of diverticulitis during the first course of chemotherapy. Four patients, whose tumors nearly disappeared after 2 courses of DCF, declined surgery and were treated with definitive chemoradiotherapy (CRT) after informed consent was obtained again after chemotherapy. Accordingly, 50 patients underwent esophagectomy after preoperative DCF (the DCF–surgery population).

Tumor Staging

All patients were evaluated using endoscopy, endoscopic ultrasonography, and FDG-PET/CT for staging. Clinical and pathologic findings were classified according to the tumor, node, metastasis classification system (TNM) (6th edition) of the International Union against Cancer (UICC).[16]

Response Evaluation

Clinical response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 by spiral computed tomography images for 54 patients who completed 2 courses of DCF.[17] Metastatic lymph nodes were used as measurable target lesions in all cases. FDG-PET/CT was performed between day 14 and day 21 after the second course of DCF in all but 1 patient. Pathologic response was evaluated according to the Japanese Classification of Esophageal Cancer (10th edition) as follows: grade 0, no recognizable cytological or histological therapeutic effect is observed; grade 1a, viable cancer cells account for two-thirds or more of the tumor tissue; grade 1b, viable cancer cells account for between one-third and two-thirds of the tumor tissue; grade 2, viable cancer cells account for less than one-third of the tumor tissue; grade 3, no viable cancer cells are apparent (pathologic complete response; pCR).[18]

Follow-Up

Follow-up of the patients was carried out at our clinic every 3 months. All patients were followed for more than 24 months, and the median follow-up period from the beginning of chemotherapy to death or the last visit was 31.1 months.

TABLE 1 Characteristics of patients who underwent esophagectomy after receiving docetaxel/cisplatin/5-fluorouracil

Characteristic	Variable	Value
Age, year	Mean ± SD (range)	67.4 ± 7.5 (52–81)
Sex	Male	46 (92 %)
	Female	4 (8 %)
Location	Upper	9 (18 %)
	Middle	26 (52 %)
	Lower	15 (30 %)
Histology	Squamous cell carcinoma	48 (96 %)
	Adenocarcinoma	2 (4 %)
Histologic grade	G1	3 (6 %)
	G2	29 (58 %)
	G3	11 (22 %)
	GX	7 (14 %)
cT	T1	6 (12 %)
	T2	10 (20 %)
	T3	33 (66 %)
	T4	1 (2 %)
cN	N1M0	33 (66 %)
	M1Lym	17 (34 %)
	M1a/M1b	6 (12 %)/11 (22 %)
cStage (TNM6)	IIB	10 (20 %)
	III	23 (46 %)
	IVA	6 (12 %)
	IVB	11 (22 %)
Type of esophagectomy	Three-phase	48 (96 %)
	Ivor-Lewis	1 (2 %)
	Transhiatal	1 (2 %)
Lymphadenectomy	Three-field	39 (78 %)
	Extended 2-field	10 (20 %)
	One-field	1 (2 %)
No. of retrieved nodes	Mean ± SD (range)	53.1 ± 17.6 (26–92)
Residual tumor	R0	41 (82 %)
	R1	8 (16 %)
	R2	1 (2 %)

SD standard deviation, *TNM6* 6th edition of the International Union against Cancer tumor, node, metastasis classification system

Statistical Analysis

Statistical analyses were performed by the JMP 10 software program (SAS Institute, Cary, NC, USA). All quantitative data are expressed as mean ± standard deviation. Differences in clinicopathologic features were determined by the Student's *t*-test or Fisher's exact test. Changes in the maximum standardized uptake value (SUV_{max}) of primary tumors were evaluated by paired *t*-tests. Survival rates were calculated by the Kaplan–Meier method, and the statistical significance of survival differences was analyzed by the log rank test. Overall survival (OS) was defined as the time from the beginning of chemotherapy to death resulting from any cause, and DFS was defined as the time from the beginning of chemotherapy to first recurrence. The Cox proportional hazard model was used for univariate and multivariate analyses of the DFS of the 50 patients who underwent esophagectomy after preoperative DCF. A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of Patients

The characteristics of patients who underwent esophagectomy after preoperative DCF are presented in Table 1. SCC was far more frequent than adenocarcinoma (48 vs. 2 cases). Two-thirds of patients had T3 tumors, and all had nodal metastasis. Three-phase subtotal esophagectomy, Ivor-Lewis esophagectomy, and transhiatal esophagectomy were performed for 48, 1, and 1 patients, respectively. Three-field lymphadenectomy and extended two-field lymphadenectomy (including bilateral recurrent laryngeal lymph node dissection) were performed for 39 and 10 patients, respectively. The mean number of retrieved nodes was 53.1. Pathologic complete resection (R0) was achieved in 41 cases, while microscopic residual disease (R1) and macroscopic residual disease (R2) were observed in 8 and 1 cases, respectively.

Clinical and Pathologic Response to DCF

Clinical and pathologic responses to DCF are shown in Fig. 1. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 5 (9.3 %), 24 (44.4 %), 24 (44.4 %), and 1 (1.9 %) cases, respectively. The clinical response rate (cRR; CR and PR) was 53.7 %, and the disease control rate (DCR; CR, PR, and SD) was 98.1 %. Four patients, who declined surgery after effective chemotherapy, experienced CR after CRT. Grade 3, 2, 1b, and 1a responses were observed in 6 (12 %), 7 (14 %), 5 (10 %), and 32 (64 %) cases, respectively, and no case showed a grade 0 response. The pathologic response rate (pRR; grades 1b, 2, and 3) was 36 %.

Changes in the SUV_{max} of Primary Esophageal Tumors after Preoperative DCF

The changes in SUV_{max} after preoperative DCF was evaluated in 53 patients. SUV_{max} decreased in 49 (92.5 %) of 53 patients, a statistically significant reduction ($P < 0.0001$).

Downstaging

To assess downstaging, we compared clinical stage before chemotherapy with pathologic stage after esophagectomy (Supplemental Fig. 1). Downstaging of the T and N categories were observed in 22 (44 %) and 18 (36 %) cases, respectively. Downstaging of TNM stage was observed in 23 (46 %) cases.

Toxicity of DCF and Postoperative Complications

Among the ITT population, grade 3/4 neutropenia was observed in 43 patients (78.2 %), and febrile neutropenia occurred in 8 patients (14.5 %). Grade 3 appetite loss, diarrhea, and constipation were observed in 4 (7.3 %), 1 (1.8 %), and 1 (1.8 %) patients, respectively. Postoperative complications were observed in 16 (32 %) of 50 cases, and the morbidity rate was comparable to that of patients who underwent esophagectomy without preoperative treatment at our institute, as reported previously.[19] There was no treatment-related mortality.

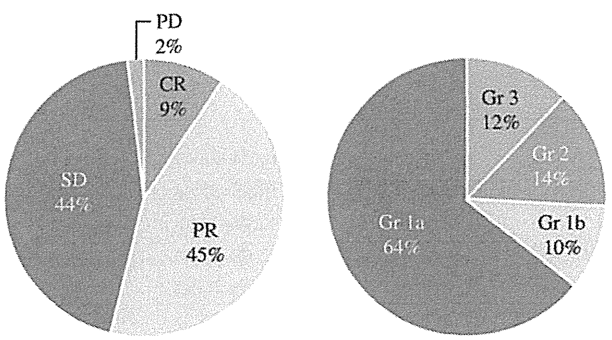


FIG. 1 Clinical and pathologic response to DCF. Clinical response was evaluated in 54 patients who completed 2 courses of DCF, while pathologic response was determined in 50 patients who underwent esophagectomy after 2 courses of DCF. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *Gr* grade

OS and DFS

Survival curves for the DCF–surgery populations are presented in Fig. 2. One- and 2-year OS were 92 and 78 %, respectively, while 1- and 2-year DFS were 68 and 56 %, respectively. In the ITT population, 1- and 2-year OS were 93 and 80 %, respectively, while 1- and 2-year DFS were 71 and 60 %, respectively (Supplemental Fig. 2).

Correlation between Response to DCF and Survival

DFS curves stratified by clinical or pathologic response are presented in Fig. 3. Clinical response significantly correlated with DFS ($P = 0.026$), and pathologic response tended to correlate with survival ($P = 0.065$).

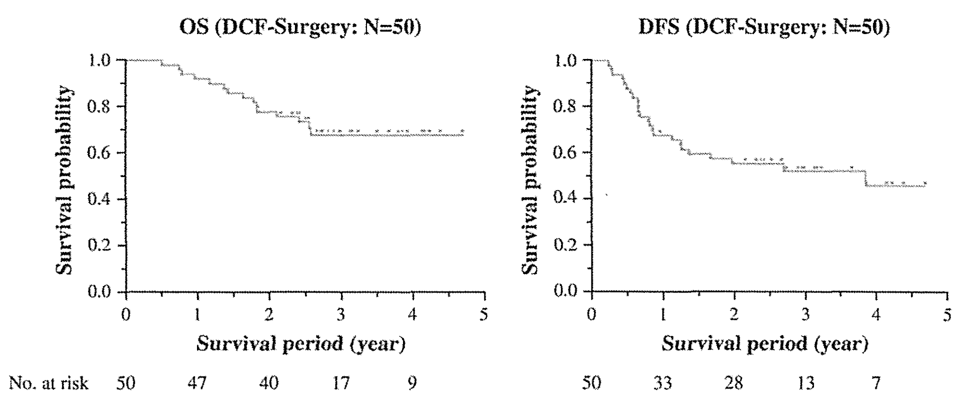
Univariate and Multivariate Analysis

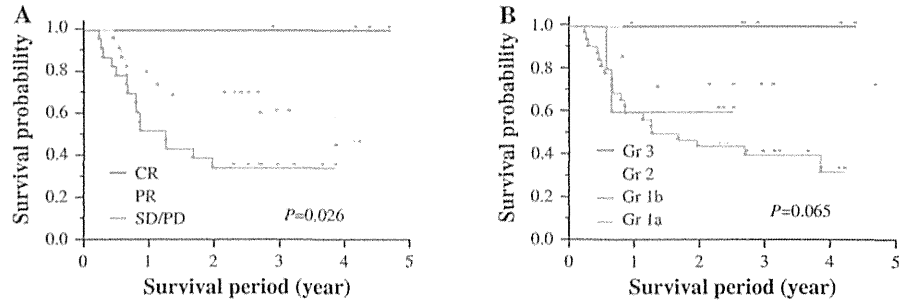
Clinical N (M1Lym), clinical response (SD/PD), ypN (N+), ypN (M1Lym), pathologic response (grade 1a), downstaging (−), and residual disease (R1/2) were significant predictors of recurrence in univariate analyses. The multivariate analysis revealed that residual tumor (R1/2; hazard ratio [HR] 5.21, 95 % confidence interval [CI] 1.64–17.2), pathologic poor response (grade 1a; HR 3.08, 95 % CI 1.08–11.1), and ypN (M1Lym; HR 13.3, 95 % CI 2.06–116) were significant independent predictors of recurrence (Table 2).

DISCUSSION

In this study, we found that preoperative DCF provided high cRR and DCR for patients with node-positive esophageal cancer, and it resulted in downstaging the disease of almost half of the patients. Two-year OS and DFS were favorable for cases of node-positive esophageal

FIG. 2 Survival curves in the population who received preoperative DCF followed by esophagectomy (DCF–surgery). OS and DFS curves are presented





No. at risk					
CR	4	4	4	3	3
PR	23	18	16	7	4
SD/PD	23	13	9	4	0

No. at risk					
Grade 3	6	5	5	2	2
Grade 2	7	6	5	2	1
Grade 1b	5	3	3	0	0
Grade 1a	32	19	14	8	3

FIG. 3 DFS, as stratified by clinical (**a**) and pathologic (**b**) response

TABLE 2 Univariate and multivariate analysis to identify predictors of recurrence

Characteristic	Object	Control	Univariate analysis		Multivariate analysis	
			Hazard ratio (95 % CI)	*P*	Hazard ratio (95 % CI)	*P*
Age	Per 1 year		0.79 (0.19–3.61)	0.76		
Sex	Male	Female	2.00 (0.30–5.84)	0.30		
Location	Upper	Middle/lower	1.61 (0.58–3.88)	0.33		
cT (T3/4)	T3/4	T1/2	1.21 (0.52–3.15)	0.66		
cN	cM1Lym	cN1M0	5.23 (2.50–14.5)	0.0019		
Clinical response	SD/PD	CR/PR	2.69 (1.18–6.47)	0.018		
ypT	ypT3/T4	ypT1/2	1.92 (0.85–4.33)	0.11	0.93 (0.34–2.64)	0.66
ypN	ypN1M0	ypN0	7.48 (2.16–47.3)	0.0005	4.74 (0.93–35.4)	0.020
	ypM1Lym		5.03 (2.16–11.8)	0.0003	13.3 (2.06–116)	
Pathologic response	Grade 1a	Grade 1b–3	3.50 (1.32–12.0)	0.0097	3.08 (1.08–11.1)	0.034
Downstaging	No	Yes	2.39 (1.03–5.99)	0.041	1.60 (0.45–5.48)	0.46
Residual tumor	R1/2	R0	8.35 (3.18–20.4)	<0.0001	5.21 (1.64–17.2)	0.0056

CI confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

cancer. In a multivariate analysis, pathologic response to DCF was a significant independent prognostic factor (along with the presence of residual tumor and ypM1 lymph node metastasis). These findings suggest that DCF is efficacious as neoadjuvant chemotherapy for node-positive esophageal cancer.

With advancements in multidisciplinary treatment, the long-term outcomes of patients with esophageal cancer have gradually been improving.[6,20] Although there is an international consensus that neoadjuvant therapy should be performed for advanced esophageal cancer, the exact target stages differ by country and region.[7,8] In the United States, the National Comprehensive Cancer Network guidelines suggest T1bN+ and T2–4a, N0–N+ as targets for neoadjuvant treatment.[21] As per the European Society for Medical Oncology guidelines, T3–4, N0–1, M0 is the indicated target of neoadjuvant therapy. In Japan, clinical stage II/III (non-T4) SCC (defined according to the UICC TNM 6th edition) is the target for neoadjuvant therapy.[14,22]

In this study, we targeted patients with node-positive esophageal cancer for preoperative DCF. This population was selected partially because favorable long-term outcomes have previously been reported for patients without lymph node metastasis. Analysis of a comprehensive registry of esophageal cancer in Japan has revealed a 65.9 % 5 years survival rate among 1097 pN0 patients treated with esophagectomy.[20] We also targeted node-positive esophageal cancer because of the JCOG 9204 study findings. JCOG 9204 compared surgery plus adjuvant chemotherapy and surgery alone for clinical stage II/III SCC of the esophagus, but it only demonstrated a survival benefit for those patients with node-positive cancers who received adjuvant therapy.[9]

Several phase 2 trials have demonstrated high response rates to DCF in cases of SCC of the esophagus.[23–26] In the current study, the cRR and pRR of DCF were 54 and 36 %, respectively, and the pCR rate was 12 %. In addition, 4 patients in the ITT cohort declined surgery after effective chemotherapy. All of these patients experienced CR with definitive CRT after DCF. The dissociation between cRR and pRR is probably due to the difficulty in pathological estimation of the pretreatment tumor extension on the resected specimens. The reduction in SUV_{max} may be a useful indicator of pathologic response. Although the DCF used in this study was a modified regimen designed to reduce toxicity, both response rates and pCR rates were much higher than those previously reported for CF.[11–13]

The multivariate analysis revealed that pathologic response was one of the independent predictors of DFS. It has previously been reported that of all patients treated with neoadjuvant CRT plus esophagectomy, only those who experience complete pathologic response obtain a survival benefit from neoadjuvant CRT.[27] However, in our study population, patients with PR appeared to obtain a survival benefit with preoperative DCF, in addition to patients with CR. This result suggests that the powerful systemic chemotherapy may contribute to control of micrometastasis from esophageal cancer.

Our multivariate analysis also revealed that R1/2 resection was an independent predictor of recurrence. Of the 9 patients in whom R0 resection could not be obtained, 5 showed residual disease at the site of primary esophageal lesions and 4 showed residual disease at the site of metastatic lymph nodes. All the former cases were of bulky tumors, and tumor shrinkage was not evident after preoperative DCF. In these cases, the circumferential resection margins were positive. Positive circumferential resection margin is known to be a significant prognostic factor in patients with esophageal cancer.[28, 29] The latter 4 cases had bulky lymph node metastases in the supraclavicular or the celiac regions. Significant shrinkage of the metastatic tumors was observed in each of these cases, but R0 resection could not be obtained because of extranodal spread of tumor cells. Extranodal spreading (or lymph node capsular invasion) has previously been described as a predictor of poor prognosis.[30, 31] For patients who have bulky esophageal tumors or bulky lymph node metastases with suspicious extranodal spreading, the choice of CRT as preoperative treatment may be more likely to result in local disease control.

There were some limitations in this study. First, this study was conducted in a single institute and was not a comparative study. A randomized controlled trial is needed to clarify the prognostic significance of preoperative DCF. Second, the DCF regimen used in this study was a reduced-dose regimen. Further analysis is needed if the dose intensity of DCF affects the prognosis of patients in neoadjuvant setting. Third, the follow-up period of 31.1 months may not be long enough to evaluate long-term survival. It is reported that more than 86 % of recurring tumors appear within 2 years after esophagectomy, and all of the patients in this study were followed up for more than 2 years.[32] Although further follow-up is needed, we suggest that preoperative DCF has at least the potential to decrease early recurrence after esophagectomy.

In conclusion, our results suggest that DCF has strong antitumor activity for esophageal cancer and may confer a survival benefit when used as preoperative chemotherapy.

DISCLOSURE The authors have nothing to disclose.

REFERENCES

1. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomized controlled trial. *Lancet*. 2002;359:1727–33.
2. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomized controlled phase III trial. *Lancet Oncol*. 2005;6:659–68.
3. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol*. 2007;25:2310–7.
4. Bedenne L, Michael P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus. *J Clin Oncol*. 2007;25:1160–8.
5. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG Trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol*. 2007;25:3719–25.
6. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junction cancer. *N Engl J Med*. 2012;366:2074–84.
7. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol*. 2007;8:226–34.
8. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol*. 2011;11:681–92.
9. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol*. 2003;21:4592–6.
10. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol*. 2012;19:68–74.
11. Igaki H, Kato H, Ando N, Shimada M, Shimizu H Nakamura T, Ozawa S, Yabusaki H, Aoyama N, Kurita A, Fukuda H. A randomized trial of postoperative chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus. Paper presented at; 2008 ASCO annual meeting.

12. Hoffman PC, Haraf DJ, Furguson MK, Drinkard LC, Vokes EE. Induction chemotherapy, surgery, and concomitant chemoradiotherapy for carcinoma of the esophagus: a long-term analysis. *Ann Oncol*. 1998;9:647–51.
13. Watanabe M, Nagai Y, Kinoshita K, et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil for patients with node-positive esophageal cancer. *Digestion*. 2011;83:146–52.
14. Tanaka T, Fujita H, Sueyoshi S, et al. Second-line combination chemotherapy with docetaxel for cisplatin-pretreated refractory-metastatic esophageal cancer: a preliminary report of initial experience. *Chemotherapy*. 2007;53:449–53.
15. Sekiguchi H, Akiyama S, Fujiwara M, et al. Phase II trial of 5-fluorouracil and low-dose cisplatin in patients with squamous cell carcinoma of the esophagus. *Surg Today*. 1999;29:97–101.
16. Sobin LH, Wittekind C. TNM classification of malignant tumors. 6th edn. New York: Wiley; 2002. p 60–5.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205–16.
18. Japan Esophageal Society. Japanese classification of esophageal cancer. 10th edn. Tokyo: Kanehara; 2008.
19. Yoshida N, Watanabe M, Baba Y, et al. Influence of preoperative chemotherapy with docetaxel/cisplatin/5-fluorouracil on the occurrence of postoperative complications after esophagectomy for patients with advanced esophageal cancer. *Dis Esophagus*. In press.
20. Tachimori Y, Ozawa S, Fujishiro M, et al. Comprehensive registry of esophageal cancer in Japan, 2006. *Esophagus*. In press.
21. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Esophageal and esophagogastric junction cancers. Version 1.2013. http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed 17 April 2013.
22. Stahl M, Budach W, Meyer HJ, et al. Esophageal cancer: clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2011;21(5):v46–9.
23. Takahashi H, Arimura Y, Yamashita K, et al. Phase I/II study of docetaxel/cisplatin/fluorouracil combination chemotherapy against metastatic esophageal squamous cell carcinoma. *J Thorac Oncol*. 2010;5:122–8.
24. Yamasaki M, Miyata H, Tanaka K, et al. Multicenter phase I/II study of docetaxel, cisplatin and fluorouracil combination chemotherapy in patients with advanced or recurrent squamous cell carcinoma of the esophagus. *Oncology*. 2011;80:307–13.
25. Osaka Y, Shinohara M, Hoshino S, et al. Phase II study of combined chemotherapy with docetaxel, CDDP, and 5-FU for highly advanced esophageal cancer. *Anticancer Res*. 2011;31:633–8.
26. Tamura S, Imano M, Takiuchi H, et al. Phase II study of docetaxel, cisplatin and 5-fluorouracil (DCF) for metastatic esophageal cancer (OGSG 0403). *Anticancer Res*. 2012;32:1403–8.
27. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg*. 2009;87:392–8.
28. Dexter SPL, Sue-Ling H, McMahon MJ, et al. Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer. *Gut*. 2001;48:667–70.
29. Chan DS, Reid TD, Howell I, et al. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. *Br J Surg*. 2013;100:456–64.
30. Tanabe T, Kanda T, Kosugi S, et al. Extranodal spreading of esophageal squamous cell carcinoma: clinicopathological characteristics and prognostic impact. *World J Surg*. 2007;31:2192–8.
31. Sakai M, Suzuki S, Sano A, et al. Significance of lymph node capsular invasion in esophageal squamous cell carcinoma. *Ann Surg Oncol*. 2012;19:1911–7.
32. Toh Y, Oki E, Minami K, et al. Follow-up and recurrence after a curative esophagectomy for patients with esophageal cancer: the first indicators for recurrence and their prognostic values. *Esophagus*. 2010;7:37–43.

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ORIGINAL ARTICLE

Risk factors for pulmonary complications after esophagectomy for esophageal cancer

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Abstract
Purpose Pulmonary complications after esophagectomy are still common and are a major cause of mortality. The aim of this study was to clarify the risk factors for the occurrence of pulmonary complications after esophagectomy.
Methods The clinical courses of 299 patients who underwent elective subtotal esophagectomy with lymph node dissection for esophageal cancer were retrospectively analyzed. Group I included patients who had pulmonary complications ($n = 53$), and group II included patients who did not ($n = 246$). The clinicopathological factors, surgical procedures and surgical results were compared between the groups.
Results The frequency of any pulmonary complication was 17.7 %. Pneumonia ($n = 26$; 8.7 %) and respiratory failure that needed initial ventilatory support for 48 h or reintubation ($n = 16$; 5.4 %) were the major morbidities. The results of the logistic regression analysis suggested that smoking with a Brinkman index ≥800, salvage esophagectomy after definitive chemoradiotherapy and the amount of blood loss/body weight were independent factors associated with the occurrence of pulmonary complications.
Conclusion Pulmonary complications after esophagectomy remain common despite advances in perioperative management. Cases with a history of heavy smoking, preoperative definitive chemoradiotherapy, and high blood loss during surgery require more careful postoperative pulmonary care.

Keywords Esophageal cancer · Surgery · Pulmonary complication · Risk factor

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Introduction

Esophagectomy for esophageal cancer is associated with higher morbidity and mortality rates (2.7–11.4 %) compared with other gastrointestinal surgeries [1–11]. In particular, postoperative pulmonary complications were reported to have incidence rates of 13–38 % [1–4, 6, 7, 11–16] and to be a major risk factor for hospital mortality [2–5, 7, 15, 17].

In Japan, the standard surgical procedure for esophageal cancer is subtotal esophagectomy with three-field lymph node dissection. This surgery is thought to be highly invasive for patients. A recently introduced minimally invasive approach, known as minimally invasive esophagectomy (MIE) [18, 19], may reduce the risk of pulmonary complications, although this remains a matter of debate. In addition, efforts to develop much less invasive surgery, such as mediastinoscopy-assisted esophagectomy, are currently being made [20].

Worldwide, a consensus has recently been reached that neoadjuvant therapy is needed for resectable advanced esophageal cancer. Neoadjuvant chemoradiotherapy (CRT) is the standard treatment in Western countries, whereas neoadjuvant chemotherapy has become the standard choice of treatment in Japan [21]. Whether the use of neoadjuvant therapies affects the occurrence of postoperative pulmonary events remains controversial.

We have a considerable interest in whether factors such as the surgical procedure and neoadjuvant therapy might affect the postoperative short-term outcomes, and, in particular, their effects on pulmonary complications. The aim of this study was to clarify the risk factors for the occurrence of pulmonary complications during recent years in a Japanese high-volume center.

Methods

A total of 368 patients underwent surgery for esophageal cancer in the Department of Gastroenterological Surgery, Kumamoto University, between April 2005 and July 2012. Patients who underwent partial esophagectomy ($n = 27$), laryngopharyngoesophagectomy ($n = 21$), transhiatal esophagectomy ($n = 14$) and two-stage esophagectomy ($n = 7$) were excluded from this study; therefore, a total of 299 patients who underwent elective subtotal esophagectomy with lymph node dissection were eligible.

For patients with node-negative tumors, we performed esophagectomy without neoadjuvant treatment. When lymph node metastases were pathologically confirmed, adjuvant chemotherapy was included. For patients with non-T4, node-positive tumors, either adjuvant (April 2005 through July 2008) or neoadjuvant (August 2008 through July 2012) chemotherapy was administered in addition to esophagectomy. For patients with T4 tumors, CRT was indicated. Definitive CRT was considered when patients preferred non-surgical treatment, regardless of the tumor stage. When the use of CRT failed to locally control the carcinoma, we recommended salvage esophagectomy. In this study, the pretreatment tumor stage was classified according to the Union Internationale Contre le Cancer TNM staging, version 6 [22]. All of the patients received bolus methylprednisolone and continuous neutrophil elastase inhibitor administration at the start of surgery to prevent respiratory failure [23]. Antibiotics were administered 30 min before surgery and every 3 hours during surgery.

We usually started surgery with simultaneous neck and abdominal manipulations. In the neck phase, mobilization of the cervical esophagus and dissection of the cervical lymph nodes were performed. When the depth of the tumor was within clinical T1, and the location was the lower esophagus, dissection of the cervical lymph nodes was omitted. Preventive dissection of the cervical lymph nodes during salvage esophagectomy was also omitted. In the abdomen phase, gastric mobilization and dissection of the abdominal lymph nodes were performed, either by a laparoscopic technique or by an open technique. A gastric tube for reconstruction was made extra-abdominally in both cases, and a retrosternal route was principally selected. If a gastric tube was not considered to be appropriate, a colonic tube was applied through the pericardial subcutaneous layer.

The anastomosis in the neck varied owing to historical differences. Most anastomoses were performed either by machine anastomosis with a circular stapler or by triangle anastomosis with linear staplers. A feeding jejunostomy was routinely placed. Thoracic manipulation was performed from the right chest either by a thoracoscopic technique or by an open technique with a small incision using thoracoscopic assists. When the depth of the tumor was suspected to be clinical T4, an open technique with a post-lateral incision was applied. Esophageal mobilization and dissection of the thoracic lymph nodes were performed with the patient in the left lateral position. The degree of mediastinal lymph node dissection was the same in cases of both superficial and advanced cancer. Preservation of the thoracic duct and right bronchial artery was performed as much as possible, except in cases with suspected direct invasion. Total MIE was defined as a surgery performed using only a laparoscopic and thoracoscopic technique, and partial MIE was defined as a surgery performed by either a laparoscopic or thoracoscopic technique. Total MIE for the clinical T1 cases was adopted from May 2011.

With regard to the definition of pulmonary complications, Cameron et al. [8] reported major morbidity after 2315 esophagectomies in accordance with the Society of Thoracic Surgeons General Thoracic Surgery Database guidelines. According to their report, a pulmonary complication was defined as the presence of one or more of the following postoperative conditions: initial ventilatory support for more than 48 h or reintubation for respiratory failure, the need for tracheostomy, pneumonia or acute respiratory distress syndrome (ARDS). Furthermore, any pulmonary complication requiring intervention or surgical treatment was added to the definition. Pneumonia was defined as the presence of new infiltrates upon chest radiography and a positive culture from the bronchoalveolar lavage. ARDS was defined as the existence of a PO_2:FiO_2 ratio less than 200 using a positive end expiratory pressure greater than 5 cmH_2O for more than 24 h, with bilateral pulmonary opacities, but without clinical suspicion of cardiac failure or fluid overload [24].

The patients were divided into two groups: group I included patients who had pulmonary complications ($n = 53$), and group II included patients who did not ($n = 246$). We retrospectively investigated the clinicopathological factors, surgical procedures and surgical results in both groups.

The statistical analysis was performed using the SPSS software program (version 13 for Windows; SPSS, Chicago, IL, USA). Statistical comparisons were performed using Student's t test or the Chi square test. After the univariate analyses, any factors that showed a $p < 0.05$

were subjected to a multivariate analysis. A $p < 0.05$ was considered to be statistically significant.

Results

The frequency of any pulmonary complication was 17.7 %. Pneumonia ($n = 26$; 8.7 %) and respiratory failure requiring initial ventilatory support for >48 h or reintubation ($n = 16$; 5.4 %) were the major morbidities. Chylothorax ($n = 9$; 3.0 %) and empyema ($n = 8$; 2.7 %) were the major pulmonary complications requiring intervention or surgical treatment.

The preoperative patient- and tumor-related factors were compared between the groups (Tables 1, 2). Smoking with a Brinkman index ≥800 (group I, 58.5 %; group II, 43.1 %; $p = 0.041$), clinical T3–T4 disease (group I, 60.4 %; group II, 38.2 %; $p = 0.003$) or T4 disease (group I, 9.4 %; group II, 2.8 %; $p = 0.027$), clinical N1 disease (group I, 67.9 %; group II, 49.6 %; $p = 0.015$) and salvage esophagectomy after definitive CRT (group I, 20.8 %; group II, 8.5 %; $p = 0.016$) were significantly associated with the occurrence of pulmonary complications. Unexpectedly, the existence of obesity, any respiratory comorbidity, chronic obstructive pulmonary disease (COPD) or diabetes mellitus did not affect the occurrence of pulmonary complications.

Table 1 Comparison of patient-related factors between the groups

Variables	Group I ($n = 53$)	Group II ($n = 246$)	p value
Age	67.2 ± 8.7	65.2 ± 9.1	0.138
Sex (Male:Female)	49:4	215:31	0.299
Body mass index (kg/m^2)	21.7 ± 3.4	21.8 ± 2.9	0.919
BMI <25:≥25	9:44	32:214	0.446
Brinkman index	840 ± 555	761 ± 626	0.412
Proportion <400:≥400	7:46	63:183	0.053
Proportion <800:≥800	22:31	140:106	0.041
Comorbidity			
Respiratory (+):(−)	19:34	61:185	0.099
COPD (+):(−)	15:38	45:201	0.099
Circulatory (+):(−)	23:30	104:142	0.881
Diabetes mellitus (+):(−)	5:48	31:215	0.520
Hepatic (+):(−)	3:50	21:225	0.485
Chronic renal failure (+):(−)	2:51	3 : 243	0.188
Central nervous system (+):(−)	7:46	16:230	0.097
Number of comorbidities	1.1 ± 1.1	1.0 ± 0.9	0.265
History of major surgery (+):(−)	7:46	37:209	0.733
ECG normal: abnormal	18:35	59:187	0.132
%VC(%) <80:≥80	50:3	237:9	0.501
FEV1 % (%) <70:≥70	36:17	184:62	0.303
Lymphocyte number (/mm^2) <1500:≥1500	23:30	142:104	0.057
Hemoglobin (mg/dL)	15:38	102:144	0.075
Male <13.5:≥13.5; female <11.4:≥11.4			
CRP (mg/L) <1.0: ≥1.0	46:7	220:26	0.578
Albumin (g/dL) <4.0:≥4.0	25:28	129:117	0.486

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiogram, *VC* vital capacity, *FEV* forced expiratory volume, *CRP* C-reactive protein

Table 2 Comparison of tumor-related factors between the groups

Variables	Group I ($n = 53$)	Group II ($n = 246$)	p value
Location			
Upper:middle:lower	10:28:15	35:130:81	0.633
Clinical T			
T1:T2:T3:T4	12:9:27:5	111:41:87:7	0.005
T1-2:T3-4	21:32	152:94	0.003
T1-3:T4	48:5	239:7	0.027
Clinical N			
N0:N1	17:36	124:122	0.015
Clinical stage			
I:II:III:IV	11:14:16:12	86:71:54:35	0.110
Preoperative treatment			
None:NAC:NACRT:dCRT	20:19:3:11	149:62:14:21	0.008
dCRT (+):(−)	11:42	21:225	0.016

NAC neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy, *dCRT* definitive chemoradiotherapy

A comparison of the surgical factors and occurrence of pulmonary complications is shown in Table 3. Although blood loss was significantly associated with the occurrence of pulmonary complications (group I, 852 ± 1249 g; group II, 554 ± 378 g; $p = 0.002$), the difference in blood loss (in grams)/body weight (in kilograms) between the groups was highly significant (group I, 15.0 ± 20.9 g/kg; group II, 9.6 ± 6.1 g/kg; $p < 0.001$). Unexpectedly, total MIE and the extent of the dissection field were unrelated. Although the length of the operation tended to be greater in group I, the difference was not significant ($p = 0.087$). While the operation during the thoracic phase under one-lung ventilation was known for 215/299 (72 %) of patients, we did not fully analyze this factor because of the existence of missing data. However, the univariate analysis of the limited data showed a significant association between the length of the thoracic operation and pulmonary complications (group I, 187 ± 92 min; group II, 152 ± 56 min; $p = 0.002$). In fact, regardless of whether the thoracic operation was performed by an open method or a

Table 3 Comparison of surgical factors between the groups

Variables	Group I ($n = 53$)	Group II ($n = 246$)	p value
Conduit			
Stomach:colon	45:8	226:20	0.114
Route			
Sub cutaneous:retrosternal: posterior mediastinal	9:37:7	29:158:59	0.180
Field of dissection 2:3	22:31	87:159	0.399
Total MIE (+):(−)	7:46	30:216	0.839
Total or partial MIE (+):(−)	9:44	44:202	0.876
Length of operation (min)	562 ± 153	533 ± 102	0.087
Length of the thoracic phase (min)[a]	187 ± 92	152 ± 56	0.002
Bleeding			
Blood loss (g)	852 ± 1249	554 ± 378	0.002
Blood loss/body weight (g/kg)	15.0 ± 20.9	9.6 ± 6.1	<0.001

[a] Data were missing for some patients

Table 4 Comparison of clinical course between the groups

Variables	Group I ($n = 53$)	Group II ($n = 246$)	p value
ICU stay (days)	4.3 ± 5.7	1.7 ± 1.5	<0.001
Duration of respirator use (days)	3.2 ± 5.4	0.6 ± 1.4	<0.001
Severity of complication (s) (Clavien-Dindo classification)			
≤IIIa:≥IIIb	30:23	135:16	<0.001
Hospital stay (days)	38.0 ± 4.6	24.0 ± 1.3	<0.001
In-hospital mortality	1	0	

ICU intensive care unit

thoracoscopic method, the length of the thoracic operation was related to the incidence of pulmonary complications ((open method) group I, 181 ± 98 min; group II, 149 ± 58 min; $p = 0.015$) ((MIE) group I, 208 ± 60 min; group II, 164 ± 46 min; $p = 0.016$).

The clinical courses were compared between the groups (Table 4). The intensive care unit (ICU) stay and the duration of respirator use were significantly longer in group I than in group II. Severe complications with a Clavien-Dindo [25] classification ≥IIIb were significantly more common in group I. Consequently, the mean hospital stay of group I was longer. Only one patient (in group I) died of respiratory failure in this study.

The results of the logistic regression analysis suggested that a Brinkman index ≥800, salvage esophagectomy and the blood loss/body weight were independent risk factors for the development of pulmonary complications (Table 5).

Discussion

Despite advances in perioperative management, pulmonary complications after esophagectomy are common, and can be a cause of hospital mortality. In the current study, the incidence of pulmonary complications was the third most common complication, following surgical site infections (30.9 %) and recurrent laryngeal nerve palsy (20.3 %). In addition, patients with pulmonary complications had significantly prolonged ICU and hospital stays, and longer durations of respirator use, resulting in high therapy costs.

The results of the multivariate analysis suggested that a Brinkman index ≥800, preoperative definitive CRT and a greater blood loss/body weight were independent risk factors for pulmonary complications. Although several risk factors have already been reported for the occurrence of pulmonary complications [1–4, 7, 12–16], they varied among studies due to differences in the study objectives, the definition of pulmonary complications and the type of surgery (Table 6). However, most previous studies have shown that smoking and/or impairment of pulmonary function are independent risk factors [1–4, 7, 12, 15, 16]. Most patients with esophageal squamous cell cancer are current or former smokers. In the current study, 86 % of the patients had a history of smoking, and 77 % of these patients had a Brinkman index ≥400. In addition, 46 % of them had a Brinkman index ≥800. A Brinkman index ≥400 relates to a risk of decreased respiratory function, whereas a value ≥800 equates to a possibility of COPD [26]. In fact, 27 % of the patients in the present study showed obstructive ventilatory impairment with a forced expiratory volume of 1.0 % <70 %. Smoking has been reported to be a risk factor for pulmonary complications, and it was also reported that tobacco cessation and preoperative respiratory rehabilitation were expected to reduce the occurrence of complications [27].

On the other hand, the existence of obesity, any respiratory comorbidity, COPD, and diabetes mellitus did not affect the occurrence of pulmonary complications in our study. It is possible that the improvements in the management of comorbidities and selection bias may be the reasons for the lack of a significant association. In particular, there have been many advances in the preoperative and postoperative management of respiratory complications, COPD and diabetes mellitus. Preoperative tobacco cessation, nasal eradication, respiratory rehabilitation, the use of long-acting β2 agonists and tight control of the perioperative blood glucose level are all rigorously enforced. The use of methylprednisolone and a neutrophil elastase inhibitor may also have contributed to the reduction of pulmonary complications [28, 29]. A recent meta-analysis suggested that the existence of obesity was not associated with the incidence of postoperative complications [30]. The current results supported the findings of this