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Preoperative Smoking Cessation and Prognosis After Curative Esophagectomy for Esophageal Cancer: A Cross-Sectional Study

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ABSTRACT

Background. Several cohort studies have reported that post-esophagectomy morbidities may worsen prognosis. Smoking cessation is an effective prophylactic measure for reducing post-esophagectomy morbidity; however, whether smoking cessation can contribute to the improvement of prognosis is unknown due to the absence of reliable databases covering the cessation period. This study aimed to elucidate whether sufficient preoperative smoking cessation can improve prognosis after esophageal cancer surgery by reducing post-esophagectomy morbidity.

Methods. This study included 544 consecutive patients who underwent curative McKeown and Ivor–Lewis esophagectomies for esophageal cancer between May 2011 and June 2021. Data on smoking status and cessation period were prospectively accumulated. Survival data were finally updated on 30 January 2022. Receiver operating characteristic curve analysis for the cut-off value of appropriate cessation period in reducing post-esophagectomy respiratory morbidity as well as analyses for the association of cessation period with short- and long-term outcomes were performed.

Results. Post-esophagectomy morbidity significantly diminished overall survival (OS) after esophagectomy ($p = 0.0003$). A short preoperative smoking cessation period of ≤ 2 months was associated with frequent post-esophagectomy morbidity of Clavien–Dindo classification $\geq$IIIb ($p = 0.0059$), pneumonia ($p = 0.016$), respiratory morbidity ($p = 0.0057$), and poor OS in clinical stages II and III ($p = 0.0015$). Moreover, it was an independent factor for poor OS (hazard ratio 1.85, 95% confidence interval 1.068–3.197; $p = 0.028$), along with body mass index <18.5 and R1 resection.

Conclusions. Sufficient preoperative smoking cessation > 2 months may be effective in improving not only short-term outcomes but also prognosis after esophagectomy for locally advanced esophageal cancer.

Esophagectomy for esophageal cancer is associated with frequent postoperative morbidities.[1] Notably, respiratory morbidity is common because patients with esophageal cancer are generally older men who have heavy smoking habits with various smoking-associated comorbidities.[2] Prophylaxis for postoperative morbidities is clinically important since post-esophagectomy morbidities may deteriorate the prognosis.[3]

Smoking cessation is an effective prophylactic measure for reducing post-esophagectomy morbidity. We have previously reported that longer durations of preoperative cessation could contribute to the reduction of respiratory morbidities after esophagectomy.[4] If postoperative respiratory morbidities decreased via smoking cessation, such cessation may help improve prognosis in esophageal cancer surgery. However, studies on the association between preoperative smoking cessation and survival after esophagectomy have seldom been published.[5]

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Thus, we prospectively collected consecutive data on smoking status and cessation period for 10 years in patients who underwent esophagectomy for esophageal cancer. Using the latest survival data, the association of the cessation period with short- and long-term outcomes after esophagectomy was investigated. The aim of this study was to elucidate whether sufficient preoperative smoking cessation can improve the prognosis after esophageal cancer surgery.

METHODS

Patients

Between May 2011 and June 2021, 688 patients underwent esophagectomy for esophageal cancer at Kumamoto University Hospital (Fig. 1). During this period, we prospectively collected consecutive data on smoking habits and the duration of smoking cessation before surgery. Of these 688 patients, 75 esophagectomies other than McKeown and Ivor–Lewis esophagectomies, 8 rare histological types, and 60 non-curative surgeries (38 clinical stage IVB and 22 R2 resections) were excluded. Additionally, imprecise data on two cessation periods and one smoking status were also excluded. All survival data were updated on 30 January 2022. Finally, 544 patients were retrospectively investigated for the association between postoperative respiratory morbidity and prognosis after esophagectomy. Moreover, 471 patients, excluding 73 non-smokers, were retrospectively investigated for the association between duration of smoking cessation and prognosis. The 8th Union for International Cancer Control TNM staging was used to determine the clinical stage.[6] Brinkman index as a smoking status was calculated as the number of cigarettes/day × duration of cessation (year). This study was conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki. The institutional Ethics Committee approved the study procedures and waived the need for written informed consent from the patients due to the retrospective nature of the study (registry number 2445).

Treatment Strategy

Solo esophagectomy with lymphadenectomy was performed for non-T4 N0 tumors. Neoadjuvant chemotherapy is generally administered for non-T4 N+ tumors, and neoadjuvant chemoradiotherapy (CRT) was administered to treat the T4 tumors. When the patient preferred non-surgical treatment, definitive CRT was considered, irrespective of the tumor stage. Salvage esophagectomy was performed for residual and recurrent tumors after definitive CRT according to the patient's wishes. Adjuvant treatment was commonly administered to patients who did not undergo preoperative treatment, and pathological lymph node metastasis was confirmed after surgery.

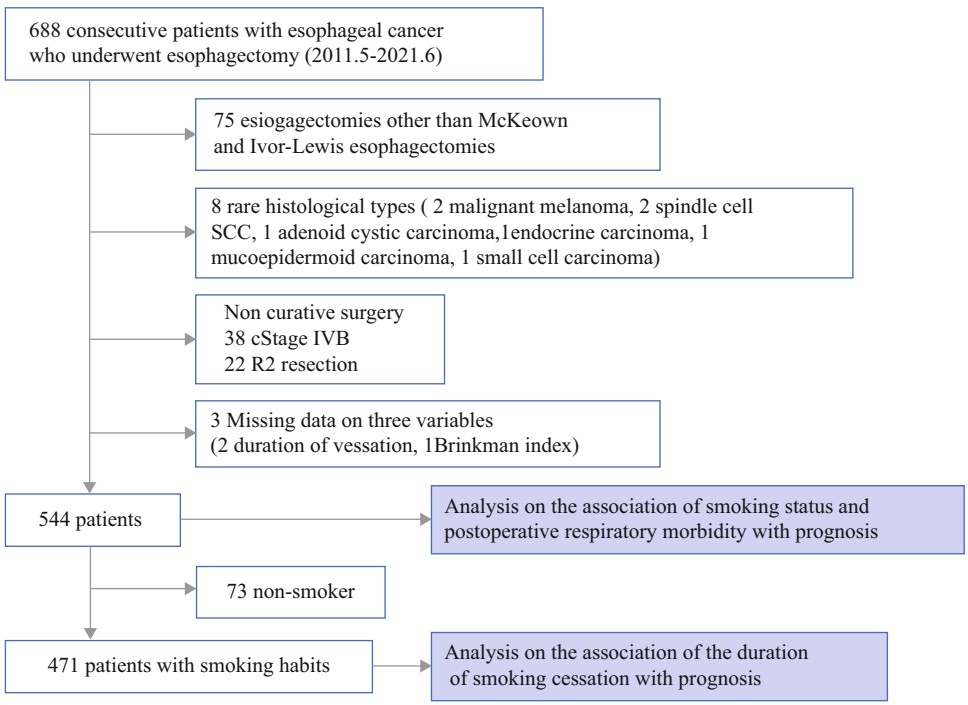

FIG. 1 Flowchart of analyzed patients. *SCC* squamous cell carcinoma

Surgery

McKeown esophagectomy was performed for tumors located in the thorax. Ivor–Lewis esophagectomy was performed for tumors located in the abdominal esophagus and did not involve lymph node metastasis in the thorax. Dissection of the esophagus and lymphadenectomy of the thorax was performed in the right thorax in all cases. Esophago-conduit anastomoses during McKeown and Ivor–Lewis esophagectomies were performed in the cervix and thorax, respectively. The extent of lymphadenectomy was determined in accordance with the 2012 guidelines prepared by the Japan Esophageal Society.[7] Minimally invasive esophagectomy was defined as an esophagectomy using thoracoscopy regardless of the use of laparoscopy and was generally performed for non-T4 tumors. Open esophagectomy was primarily performed for T4 suspicious tumors.

Definitions of Morbidities

The morbidity details have been previously described.[8] Morbidity was defined as a complication of Clavien–Dindo classification grade II or more, while respiratory morbidity was defined as a complication that met the following criteria: (1) initial ventilatory support for > 48 h or re-intubation for respiratory failure; (2) need for tracheostomy; (3) pneumonia, defined as the presence of new infiltrates on chest radiography and a positive culture of bronchoalveolar lavage; and (4) need for intervention or surgical treatment due to respiratory morbidity.

Follow-Up Evaluation

Every 1–3 months, follow-up was conducted until the end of the study period or until death. Tumor marker tests were conducted every 3 months, computed tomography was performed every 6 months, and annual endoscopy of the upper gastrointestinal tract was generally performed until 5 years after surgery. The median duration of follow-up was 1172 days in all patients and 1571 days in survivors.

Statistical Methods

Statistical analyses were performed using JMP Pro version 16 (SAS Institute, Cary, NC, USA). The Mann–Whitney U test was used to compare unpaired samples, and a two-sided Fisher's exact test was used to examine the significant differences between the groups. The cut-off value of the duration of smoking cessation was determined based on receiver operating characteristic curve (ROC) analysis and the Youden index for the incidence of postoperative respiratory morbidity. Overall survival (OS) was estimated using the Kaplan–Meier method and was compared using the log-rank test. A multivariable Cox proportional hazard model was constructed to determine the prognostic factors for OS, including age at surgery (for 5-year increase), sex (male vs. female), body mass index (BMI; <18.5 vs. ≥ 18.5), performance status (PS; 0 vs. 1 and 2), American Society of Anesthesiologists (ASA) physical status (1 and 2 vs. 3), respiratory comorbidity (vs. no), clinical stage (II vs. III), preoperative treatment (vs. no), adjuvant treatment (vs. no), pathology (squamous cell carcinoma and basaloid carcinoma vs. adenocarcinoma and adenosquamous carcinoma), field of lymphadenectomy (2 and 3 vs. 1), operation time (for 60 min increase), blood loss (for 100 g increase), R1 resection (vs. no), postoperative respiratory morbidity (vs. no), and duration of smoking cessation (≤ 2 vs. > 2 months). Any variables with a p-value < 0.10 after the univariate analysis were included in the adjusted analysis. OS was defined as the interval between the date of surgery and the date of death. Statistical significance was set at $p < 0.05$.

RESULTS

Postoperative Respiratory Morbidity and Prognosis After Esophagectomy

Kaplan–Meier analysis including all patients (both smokers and non-smokers) suggested that postoperative respiratory morbidity caused OS to significantly worsen ($p = 0.0003$) (Fig. 2a). Similar results were only obtained in smokers ($p = 0.0038$) (Fig. 2b). Meanwhile, the difference in OS between smokers and non-smokers was statistically equivalent ($p = 0.39$), regardless of clinical stage (electronic supplementary Fig. 1).

Determination of the Cut-Off Value of the Duration of Preoperative Smoking Cessation

ROC analysis for the incidence of postoperative respiratory morbidity in four clinically feasible periods of cessation (2 weeks, 1 month, 2 months, and 3 months) was performed (electronic supplementary Table 1). Based on the maximal Youden index, 2 months was determined as the cut-off value for appropriate smoking cessation.

Clinicopathological and Treatment Features in Smokers

Table 1 shows the clinicopathological and treatment features in patients with a smoking habit, in accordance with the cessation period. In the short-cessation group (≤ 2

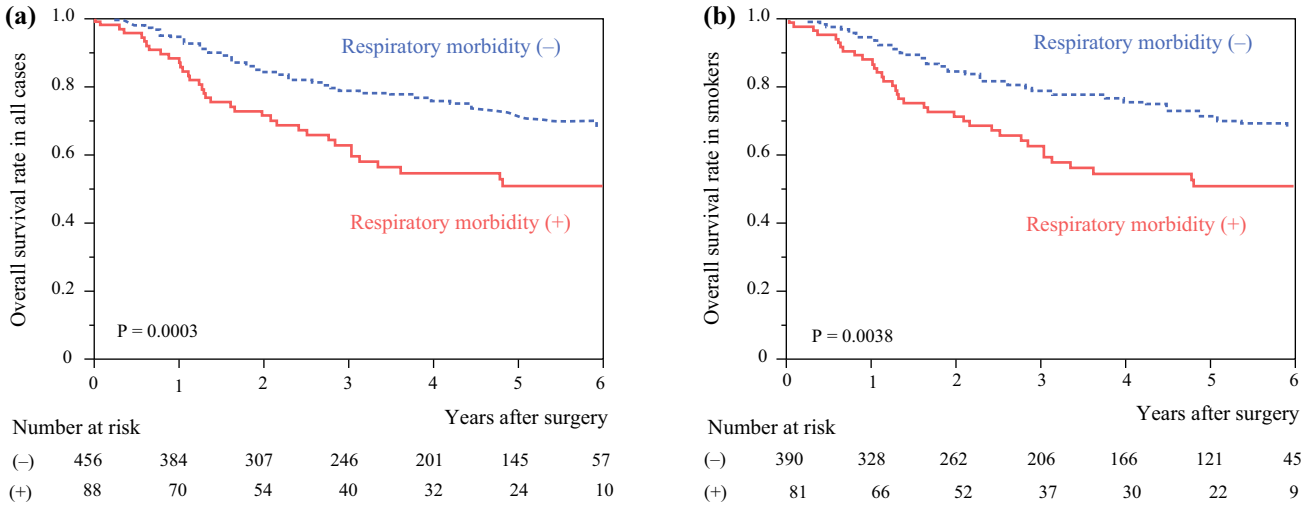

FIG. 2 Kaplan–Meier curves of **a** overall survival and **b** relapse-free survival in all patients in accordance with the incidence of postoperative respiratory morbidity

months), age at surgery was lower and the prevalence of respiratory comorbidity was higher than that in the long-cessation group. Additionally, the clinical stage was earlier, thus preoperative treatment was less frequently administered. Severe postoperative morbidity ($p = 0.0059$), respiratory morbidity ($p = 0.0057$), and pneumonia ($p = 0.016$) were significantly more frequent in the short-cessation group.

Overall Survival After Esophagectomy in Accordance with Duration of Smoking Cessation

Because the clinical stage significantly differed between the groups, prognostic analyses were separately performed for clinical stages I, II and III, and IVA. The preoperative short cessation period did not reduce OS when analyzed in all patients (Fig. 3a), and did not affect OS in clinical stage I or IVA (Fig. 3b, d). Meanwhile, a short cessation period significantly reduced OS in clinical stages II and III (median survival 27 vs. 34 months; 5-year survival rate 41% vs. 66%; $p = 0.0015$) (Fig. 3c).

Prognostic Factors in Esophagectomy in Clinical Stages II and III

Cox regression analysis for OS suggested that the short cessation period was an independent factor for poor prognosis in clinical stages II and III (hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.068–3.197; $p = 0.028$), along with BMI <18.5 (HR 1.94, 95% CI 1.031–3.633; $p = 0.040$) and R1 resection (HR 4.19, 95% CI 1.283–13.651; $p = 0.018$) (Table 2).

DISCUSSION

Prophylactic measures for reducing post-esophagectomy morbidity are important because of their effect on both short- and long-term outcomes.[3] Smoking cessation is one of the most effective preoperative prophylactic measures employed; however, studies on the appropriate duration of cessation for the reduction of post-esophagectomy morbidities have seldom been published.[4,5,9] The primary reason for the lack of such studies is the absence of reliable clinical databases covering the cessation period. Thus, we prospectively accumulated consecutive data on smoking status, cessation period for 10 years, and updated survival. In the present study, several remarkable results were obtained. First, post-esophagectomy respiratory morbidity worsens prognosis. Second, a short cessation period of ≤ 2 months significantly increased respiratory morbidity, pneumonia, and severe morbidity. Third, a short cessation period was found to be a possible independent factor for poor prognosis in clinical stages II and III, namely locally advanced esophageal cancer. Fourth, it did not affect the prognosis in clinical stages I and IVa.

Only one retrospective study by Kamarajah et al. has investigated the association of preoperative smoking cessation with prognosis after esophagectomy. In the study, smoking cessation > 6 weeks did not improve prognosis after Ivor–Lewis esophagectomy[5]; however, appropriate duration of cessation and prognosis for each cancer stage were not analyzed. In the present study, most esophagectomies performed were McKeown esophagectomies, which are highly invasive and associated with frequent postoperative morbidities compared with Ivor–Lewis esophagectomy. The appropriate cessation period for postoperative respiratory morbidity was determined by

TABLE 1 Clinicopathological and treatment features in patients with smoking habits

Clinical, epidemiological, or pathological feature	Total *N*	Duration of smoking cessation		*p*-Value
		≤ 2 months	> 2 months	
All cases	471	151	320	
Age at surgery, years [mean ± SD]	66.0 ± 8.0	63.8 ± 8.0	67.0 ± 7.8	< 0.0001
Sex, male	419 (89)	133 (88)	286 (89)	0.75
Body mass index[a] [mean ± SD]	20.4 ± 3.5	21.4 ± 3.4	22.0 ± 3.0	0.035
<18.5	64 (14)	30 (20)	34 (11)	0.024
18.5–25.0	334 (71)	99 (66)	235 (73)	
25.0<	73 (15)	22 (15)	51 (16)	
Brinkman index[a] [mean ± SD]	880 ± 500	930 ± 390	860 ± 540	0.14
Performance status				0.86
0	430 (91)	137 (91)	293 (92)	
1<	41 (9)			
ASA physical status				1.0
1 and 2	446 (95)	143 (95)	303 (95)	
3	25 (5)	8 (5)	17 (5)	
Comorbidity				
Diabetes mellitus	110 (23)	32 (21)	78 (24)	0.48
Respiratory disease	173 (37)	66 (44)	107 (33)	0.032
Cardiovascular disease	268 (57)	78 (52)	190 (59)	0.13
Location of tumor				0.86
Ce	2 (0.4)	1 (1)	1 (0.3)	
Ut, Mt, Lt	448 (95)	143 (95)	305 (95)	
Ae	21 (4)	7 (5)	14 (4)	
Clinical stage				< 0.0001
I	211 (45)	91 (60)	120 (38)	
II	85 (18)	21 (14)	64 (20)	
III	136 (29)	32 (21)	104 (33)	
IV	39 (8)	7 (5)	32 (10)	
Pathology				0.42
Squamous cell carcinoma	420 (89)	132 (87)	288 (90)	
Adenocarcinoma	41 (9)	17 (11)	24 (8)	
Basaloid carcinoma	7 (1)	1 (1)	6 (2)	
Adenosquamous cell carcinoma	3 (1)	1 (1)	2 (1)	
Neoadjuvant treatment				< 0.0001
None	261 (55)	108 (72)	153 (48)	
Chemotherapy	142 (30)	34 (23)	108 (34)	
NACRT	55 (12)	5 (3)	50 (16)	
Definitive CRT	13 (3)	4 (3)	9 (3)	
Surgical procedure				0.22
McKeown esophagectomy	464 (99)	147 (97)	317 (99)	
Ivor–Lewis esophagectomy	7 (1)	4 (3)	3 (1)	
MIE	117 (25)	35 (23)	82 (26)	0.65
Operation time, min [mean ± SD]	570 ± 110	570 ±110	570 ± 110	0.66
OE	560 ± 130	560 ± 140	550 ± 130	0.95
MIE	580 ± 110	580 ± 110	570 ± 110	0.65
Blood loss, g[b] [mean ± SD]	330 ± 500	300 ± 350	340 ± 560	0.39
OE	630 ± 820	620 ± 510	630 ± 900	0.95
MIE	230 ± 280	200 ± 200	240 ± 320	0.25

Table 1 (continued)

Clinical, epidemiological, or pathological feature	Total *N*	Duration of smoking cessation		*p*-Value
		≤ 2 months	> 2 months	
R1 resection	10 (2)	2 (1)	8 (3)	0.51
Postoperative morbidity				
Any morbidity, CDc ≥II	174 (37)	63 (42)	111 (35)	0.15
Severe morbidity, CDc ≥IIIb	57 (12)	28 (19)	29 (9)	0.0059
Respiratory morbidity	81 (17)	37 (25)	44 (14)	0.0057
Pneumonia	50 (11)	24 (16)	26 (8)	0.016
Cardiovascular morbidity	36 (8)	10 (7)	26 (8)	0.71
Leak	57 (12)	18 (12)	39 (12)	1.0

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *ASA* American Society of Anesthesiologists, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *Ae* abdominal esophagus, *NACRT* neoadjuvant chemoradiotherapy, *CRT* chemoradiotherapy, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *CDc* Clavien–Dindo classification

[a]The Brinkman index was calculated as follows: (cigarette number/day) × year

[b]Two outliers due to intraoperative accidents (16,110 g in OE and 26,216 g in MIE) were excluded

ROC analysis, and the prognoses for each clinical stage were investigated. Several preoperative prophylaxes, such as nutritional intervention,[10] respiratory rehabilitation,[11] and oral hygiene,[12] are commonly suggested as useful actions for reducing postoperative morbidity. However, no studies have elucidated that such prophylaxes can improve prognosis. To the best of our knowledge, this is the first study to clarify the importance of preoperative smoking cessation in the improvement of long-term outcomes in esophagectomy.

In this study, the survival benefit of smoking cessation was only ascertained in esophageal cancer in clinical stages II and III. Persistent inflammation during morbidity weakens host immunity against cancer, which can result in the proliferation of residual micro cancer cells after surgery.[13] This mechanism can affect early-stage cancer only weakly because early-stage cancer is likely to be completely resected by surgery and the amount of residual cancer cells is considerably small. This may explain the absence of a survival benefit associated with smoking cessation in clinical stage I esophageal cancer. Prognosis in far-advanced cancer may also be affected by smoking cessation and subsequent postoperative morbidity via proliferation of residual cancer cells. However, advanced cancer primarily has a high risk of recurrence, irrespective of the incidence of respiratory morbidity. This may be a reason for the absence of a survival benefit associated with cessation in clinical stage IVa. Non-association between the appropriate duration of smoking cessation to reduce respiratory morbidity and prognosis in clinical stage I and IVa were reconfirmed via additional analyses (electronic supplementary Figs. 2 and 3).

Other mechanisms may also be involved in poor prognosis for patients with a short cessation period. Frequent postoperative morbidity due to insufficient cessation often delays physical recovery and decreases activities of daily living (ADLs).[14] Decreased ADLs can increase deaths from diseases other than esophageal cancer, such as aspiration pneumonia and traumatic injury. Moreover, decreased ADL and frequent comorbidity can affect treatment strategies for recurrence after surgery, and patients with these disadvantages often cannot receive intensive treatments, which can also worsen prognosis. The short-cessation group in this study was significantly related to low BMI and frequent respiratory comorbidities. Several studies have suggested that low BMI, malnutrition, and respiratory comorbidity can also cause postoperative morbidity and poor prognosis.[15–17]

In this study, preoperative smoking cessation > 2 months is recommended to improve surgical outcomes; however, there is a clinical problem based on whether preoperative cessation > 2 months is possible in locally advanced esophageal cancer surgery. The standard treatment for locally advanced esophageal cancer is neoadjuvant treatment and subsequent esophagectomy.[18–20] The duration between neoadjuvant treatment and esophagectomy is usually approximately 2 months. If patients are educated on the importance of smoking cessation at the first visit, a preoperative cessation > 2 months is achievable. We believe that the present results can help physicians elucidate the extent to which smoking cessation before esophagectomy positively affects prognosis and to encourage patients to pursue quitting smoking.

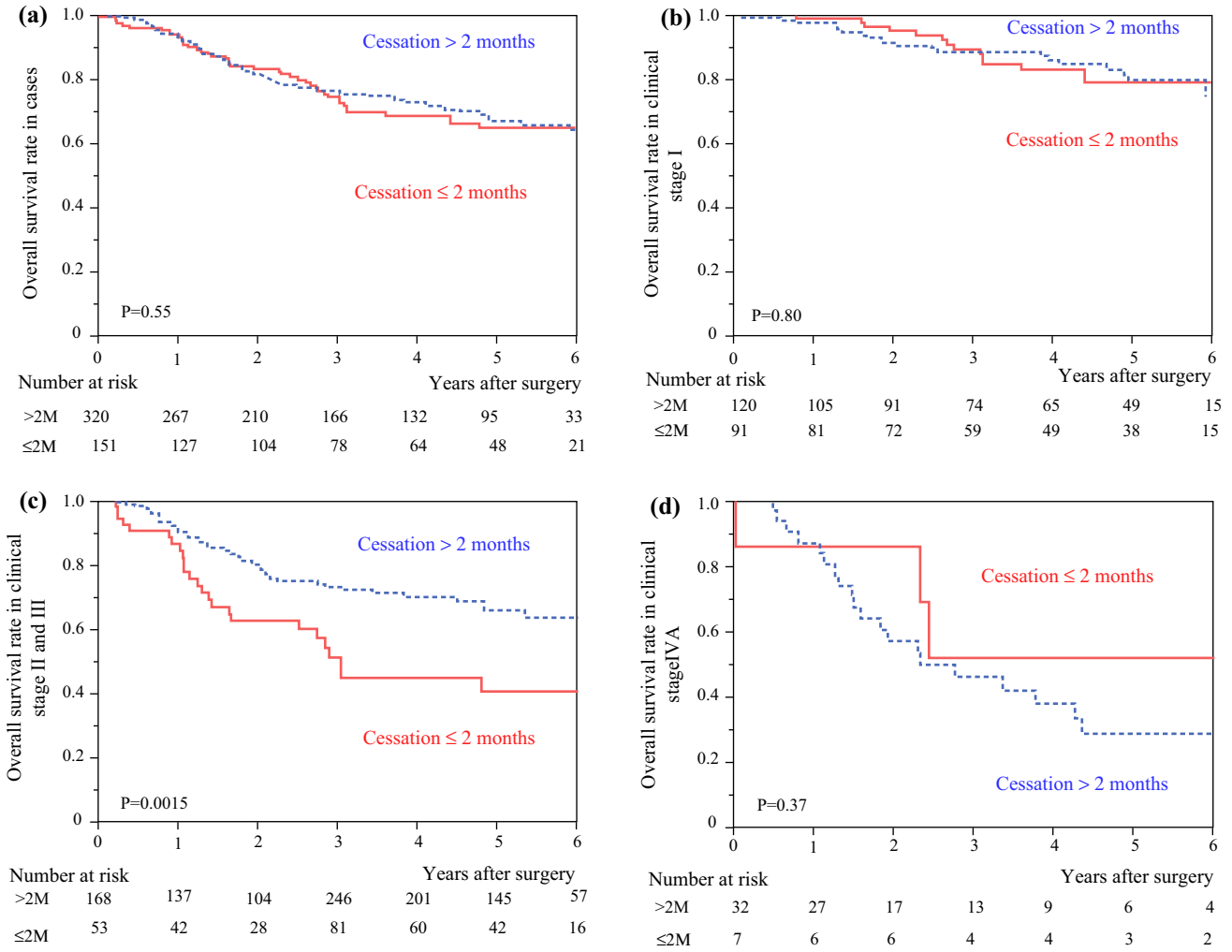

FIG. 3 Kaplan–Meier curves of overall survival in **a** all patients, **b** clinical stage IB, **c** clinical stage II and III, and **d** clinical stage IVA in accordance with the duration of smoking cessation

Based on this study, prophylaxis for postoperative morbidity in patients with insufficient smoking cessation has been found to be important. First, to ensure patient smoking cessation, measuring the exhaled carbon monoxide may be useful because it can reflect smoking status and predict the incidence of post-esophagectomy morbidity.[21] If a patient does not quit smoking, surgeons may even elect to offer surgery postponement. If the effect of preoperative treatment is good (near-complete response and partial response), the extension of surgery may be tolerable. In cases where it is not good, the surgeon may have to perform surgery at a high risk of respiratory morbidity. In such cases, various prophylaxes, such as nutritional intervention,[10] perioperative rehabilitation,[11] use of an enhanced recovery after surgery program,[22] perioperative management by a multidisciplinary care team,[23,24] and further less invasive surgical procedures,[25,26] may be effective in reducing morbidities.

The clinical significance of this study is to first provide a novel possibility of preoperative prophylactic measures for improving prognosis in esophagectomy. The present results may support various efforts to reduce post-esophagectomy morbidity and reinforce the importance of data accumulation in this field. Thus, further studies using larger cohorts, such as a national clinical database or international study group database, are expected to strengthen and verify the current results.

Despite thoughtful analyses using prospectively collected and reliable data, this study has several limitations. The biggest limitation is the ambiguity of the duration of smoking cessation obtained via interviews with patients and their families; however, it is difficult to objectively and precisely determine the cessation period using other methods. Moreover, due to the nature of a single-institute

TABLE 2 Cox regression analysis for overall survival after esophagectomy in clinical stages II and III esophageal cancer

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age at surgery (for 5-year increase)	1.05 (0.913–1.210)	0.48		
Male sex (vs. female sex)	1.28 (0.585–2.791)	0.54		
Body mass index <18.5 (vs. ≥18.5)	2.19 (1.234–3.875)	0.0073	1.94 (1.031–3.633)	0.040
Performance status 0 (vs. 1 and 2)	0.91 (0.395–2.104)	0.83		
ASA physical status 1 and 2 (vs. 3)	0.52 (0.208–1.291)	0.16		
Respiratory comorbidity	1.32 (0.821–2.113)	0.25		
Clinical stage II (vs. stage III)	0.71 (0.433–1.160)	0.17		
Preoperative treatment (vs. no)	1.18 (0.707–1.977)	0.52		
Adjuvant treatment (vs. no)	1.31 (0.742–2.320)	0.35		
Pathology, squamous cell and basaloid carcinoma (vs. adenocarcinoma and adenosquamous carcinoma)	0.69 (0.360–1.307)	0.25		
Field of lymphadenectomy 2 and 3 (vs. 1)	0.54 (0.247–1.188)	0.16		
Operation time (for 60 min increase)	0.96 (0.842–1.089)	0.55		
Blood loss (for 100 g increase)	1.01 (0.998–1.012)	0.093	1.01 (0.999–1.013)	0.085
R1 resection (vs. R0)	2.96 (0.929–9.454)	0.066	4.19 (1.283–13.651)	0.018
Postoperative respiratory morbidity (vs. no)	1.55 (0.924–2.602)	0.097	1.36 (0.765–2.427)	0.29
Duration of smoking cessation ≤ 2 months (vs. > 2 months)	2.15 (1.323–3.482)	0.0020	1.85 (1.068–3.197)	0.028

HR hazard ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists

cohort study, several historical biases exist with regard to perioperative management and treatment, and advances in drugs and equipment, among others.

CONCLUSION

Sufficient preoperative smoking cessation > 2 months may be effective in improving not only short-term outcomes but also the prognosis after curative esophagectomy for locally advanced esophageal cancer. We believe that this study can help convey the importance of smoking cessation to patients who undergo esophagectomy, and to contribute to the improvement of prognosis in esophageal cancer surgery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-022-12433-z.

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