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Preoperative Smoking Cessation is Integral to the Prevention of Postoperative Morbidities in Minimally Invasive Esophagectomy

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Abstract

Background Preoperative smoking cessation is considered integral to decreasing postoperative morbidities after esophagectomy. To our knowledge, the association of the duration of smoking cessation with the occurrence of postoperative morbidity has never been investigated in minimally invasive esophagectomy (MIE).

Methods A total of 198 consecutive MIEs for esophageal cancer between June 2011 and December 2017 were eligible for the study. According to the length of smoking cessation, patients were separated into three groups: \leq 30, 31–90, and > 91 days. Incidence of postoperative morbidities was retrospectively analyzed among the groups.

Results In patients with smoking cessation ≤ 30 days, morbidities of Clavien–Dindo classification (CDc) \geq II, severe morbidities of CDc \geq IIIb, pneumonia, and any pulmonary morbidities were frequently observed. Morbidities of CDc \geq II, pneumonia, and any pulmonary morbidities increased as the length of cessation became shorter. Smoking cessation ≤ 30 days was a significant risk factor for severe morbidity (hazard ratio [HR] 4.89, 95% confidence interval [CI] 1.993–12.011; P < 0.001). Smoking cessation ≤ 90 days (HR 3.98, 95% CI 1.442–10.971; P = 0.008), past smoking (per 100 increase in Brinkman index), and cardiovascular comorbidity were significant risk factors for pneumonia. Smoking cessation ≤ 30 days (HR 3.13, 95% CI 1.351–7.252; P = 0.008) and past smoking were significant risk factors for any pulmonary morbidity.

Conclusions Preoperative smoking cessation is considerably important to prevent postoperative morbidities, even in MIE. At least, preoperative cessation ≥ 31 days is preferable to decrease considerable morbidities after MIE.

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Introduction

Esophagectomy for esophageal cancer is associated with high incidences of postoperative morbidities [1–4]. Notably, pulmonary and infectious complications are frequent and are the leading causes of operation-related mortality after esophagectomy [5–8]. Those morbidities may also correlate with poor long-term outcomes [9–11]. Thus, reducing postoperative morbidities is important to improve both short-term and long-term outcomes after esophagectomy.

Minimally invasive esophagectomy (MIE) is widely accepted as a less invasive surgery compared with open esophagectomy (OE). One prospective randomized controlled trial (RCT) and two meta-analyses demonstrated the superiority of MIE regarding the incidence of postoperative morbidities [12–14]. On the other hand, several retrospective studies based on large nationwide clinical databases could not prove the superiority [1, 15]. Thus, whether MIE truly correlates with the reduction of morbidity is debatable.

To date, many studies suggested that smoking is an independent risk factor for the occurrence of morbidities after esophagectomy [3, 6–8, 16]. In patients who continue to smoke, preoperative smoking cessation is important to decreasing morbidities after esophagectomy [17]. However, most of those studies were mainly designed for patients undergoing OE. It is unclear how preoperative smoking and cessation affect the postoperative course in MIE. Thus, this study aimed to investigate the association between duration of preoperative smoking cessation and the incidence of morbidities after MIE. In addition, we elucidated the adequate duration of cessation to prevent postoperative morbidities.

Materials and methods

Patients

Two hundred and thirty-three consecutive patients who underwent elective MIE for esophageal cancer at Kumamoto University Hospital between June 2011 and December 2017 were eligible. Five patient who underwent salvage esophagectomy after definitive chemoradiotherapy was excluded from this study. During their admission for surgery, we routinely asked patients about their past history of smoking and duration of cessation. According to the duration of cessation, 198 patients with past smoking were separated into three groups: \leq 30, 31–90, and \geq 91 days. An optimal length of cessation to prevent complications after esophagectomy has rarely been investigated. We referred to previous studies and attempted to identify an optimal duration of smoking cessation that was applicable to/utilized in thoracic surgery. We observed that cessation for 30 days was the most frequently adopted duration to investigate the usefulness of preoperative smoking cessation [18, 19]. A study performed by Ngaage et al. [20] reported smoking cessation over a 90-day duration to investigate the occurrence of pulmonary complications after cardiac surgery. Finally, the incidence of postoperative morbidity was retrospectively investigated among the groups in order to elucidate which duration of smoking cessation could significantly reduce postoperative morbidity. In addition, the incidence of postoperative morbidity was also investigated in 30 never-smokers. The study procedures were approved by our institutional review board (Registry Number 1459). Documented consent was obtained from each patient.

Treatment strategy and surgery

The pretreatment tumor stage was assessed in accordance with the Cancer Staging Manual, version 7 [21]. For tumors in clinical stage 0 and IA, we performed esophagectomy without neoadjuvant treatment. For tumors in clinical stage IB, II, and III, neoadjuvant chemotherapy (NAC) or neoadjuvant chemoradiotherapy (NACRT) were administered before esophagectomy. In this study, all patients underwent MIE. MIE was defined as an esophagectomy performed using only thoracoscopy, regardless of laparoscopy use. Manipulation in the chest was implemented from the right thorax in the left hemiprone position. The extent of lymphadenectomy was determined in accordance with the 2012 guidelines of the Japan Esophageal Society [22]. A three-field lymphadenectomy was principally conducted for tumors in the upper- and middle-thoracic esophagus. Cervical lymph node dissection was omitted for T1 tumors in the lower esophagus.

Perioperative managements

Methylprednisolone (bolus) and neutrophil elastase inhibitors (continuous intravenous administration for 24 h) were routinely administered at the onset of surgery. Antibiotics were also administered every 4 h intraoperatively. Extubation was principally performed immediately following surgery in the operating room. Patients were usually observed in the intensive care unit for only a day postoperatively. Postoperative rehabilitation was initiated by a physical therapist a day after the surgery. Enteral nutrition was routinely initiated a day after the surgery. The perioperative management protocol remained unchanged during the study period.

Definition of morbidities

Morbidities were decided in accordance with the definitions proposed by the Society of Thoracic Surgeons General Thoracic Surgery [23]. The details of the morbidities are available elsewhere [24]. Any morbidity and severe morbidity constitutes any conditions with a Clavien–Dindo classification (CDc) \geq II and \geq IIIb, respectively [25].

Statistical methods

The statistical analysis was performed with aid of the software package StatViewTM version 5.0 created by Abacus Concepts, Inc., Berkeley, CA, USA. Comparisons

between the groups were conducted using the Chi-square test. For comparisons of unpaired samples, the Mann-Whitney U test or Student's t test were conducted. Multivariate analysis was performed for severe morbidity, pneumonia and any pulmonary morbidity. The following elements were assessed for the independent risk factors for those morbidities: age at surgery (per 10 years), sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. \geq 1), body mass index (< 18.5 vs. \geq 18.5 kg/m²), past smoking [Brinkman index, year x number/day (number-years)], duration of smoking cessation, American Society of Anesthesiologists Physical Status (ASAPS) (1 vs. \geq 2), presence of diabetes mellitus, respiratory comorbidities, cardiovascular comorbidities, % volume capacity (VC) ($< 80 \text{ vs.} \ge 80\%$), forced expiratory volume (FEV) 1% (< 70 vs. > 70%), clinical T stage (T1, 2 vs. T3, 4), clinical N stage (N0 vs. N1-3), preoperative treatment (present vs. absent), operative time (per 60 min), intraoperative bleeding (per 100 g), and use of laparoscopy (yes vs. no). The factors at a probability level ≤ 0.1 were used for subsequent multivariate analysis. Significant risk factors were taken to be at a probability level < 0.05 in logistic regression analysis.

Results

Clinical features of patients

Patients' characteristics are listed in Table 1 in accordance with the length of cessation. A total of 198 patients with past smoking, 180 (90.9%) were males. The overall average age in patients who had stopped smoking \geq 91 days was significantly higher than those in other groups. NAC and NACRT were performed in 44 and 6 patients, respectively. Forty-five (22.7%) patients had diabetes mellitus. Fifty-seven (28.8%) and 111 (56.1%) patients had respiratory and cardiovascular comorbidity, respectively. There were no significant differences in the incidence of those comorbidities among groups. One hundred and fiftyseven (79.3%) patients underwent laparoscopic surgery in the abdomen.

Relation between length of cessation and morbidity

Table 2 shows postoperative morbidities after MIE in accordance with the duration of cessation. In patients with smoking cessation ≤ 30 days, morbidities of CDc \geq II, severe morbidities of CDc \geq IIIb, pneumonia, any pulmonary morbidities were frequently observed than those in other groups. Any morbidities of CDc \geq II increased as the length of cessation became shorter. Pneumonia and any pulmonary morbidity significantly frequently occurred as

the length of cessation became shorter. In patients who had stopped smoking ≥ 31 days, the incidence of severe morbidity reduced to as low as that of a person who had never smoked. In patients who had stopped smoking ≥ 91 days, the occurrence of pneumonia also reduced to as low as that of a person who had never smoked.

Risk factor for postoperative morbidities

Analyses of factors correlated with severe morbidity, pneumonia, and any pulmonary morbidity are shown in Tables 3, 4, and 5 [only in patients with past smoking (n = 198)]. Smoking cessation ≤ 30 days was a significant risk factor for severe morbidity (hazard ratio [HR] 4.89, 95% confidence interval [CI] 1.993–12.011; P < 0.001). Smoking cessation < 90 days was also a significant risk factor for pneumonia (HR 3.98, 95% CI 1.442-10.971; P = 0.008), as well as past smoking (per 100 increase in Brinkman index, HR 1.10, 95% CI 1.001–1.209; P = 0.047) and cardiovascular comorbidity (HR 3.09, 95%) CI 1.037–9.186; P = 0.043). Regarding any pulmonary morbidity, smoking cessation < 30 days was a significant risk factor (HR 3.13, 95% CI 1.351-7.252; P = 0.008), as well as past smoking (per 100 increase in Brinkman index, HR 1.09, 95% CI 1.009–1.183; P = 0.029).

Discussion

In this study, several interesting results were obtained regarding duration of preoperative cessation and the occurrence of morbidity after MIE. First, in patients with short duration of cessation ≤ 30 days, morbidities of CDc > II, severe morbidities of CDc > IIIb, pneumonia, and any pulmonary morbidities were frequently observed. Second, the occurrence of severe morbidity in patients who had stopped smoking ≥ 31 days reduced to as low as that of a person who had never smoked. The incidence of pneumonia in patients who had stopped smoking \geq 91 days also reduced to as low as that of a person who had never smoked. Third, smoking cessation \leq 30 days was a significant risk factor for severe morbidity and any pulmonary morbidity. Smoking cessation ≤ 90 days was also a significant risk factor for pneumonia.

Smoking can induce postoperative morbidities via several mechanisms. It correlates with peripheral bronchoconstriction [26], decline in diffusing capacity, and increased respiratory secretion [27], which can result in pulmonary morbidity. Smoking also induces inflammation and tissue hypoxia, which increase the risk of postoperative wound dehiscence and infection [28, 29]. Smoking cessation abates the bronchial hyper-responsiveness and

Table 1	Characteristics	of patients	according to th	e duration of	smoking cessation
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Variables		Duration of smoking cessation				
		\leq 30 days (n = 42)	31–90 days $(n = 48)$	\geq 91 days (n = 108) 66.4 \pm 7.1*#		
Age	Years old	$62.7 \pm 8.4*$	$63.6 \pm 6.8 $ #		0.008*	
					0.020#	
Sex	Male: female	38: 4	43: 5	99: 9	0.911	
BMI	$< 18.5: 18.5-24.9: \ge 25 \text{ kg/m}^2$	5: 30: 7	5: 33: 10	6: 81: 21	0.674	
Brinkman index	$1-399: 400-799: \ge 800$	4: 12: 26	2: 15: 31	23: 38: 47	0.019#	
Performance status	0: 1: 2	38: 3: 1	44: 4: 0	105: 3: 0	0.171	
ASAPS	1: 2: 3	8: 34: 0	10: 35: 3	21: 84: 3	0.529	
Diabetes mellitus	Present: absent	9: 33	12: 36	24: 84	0.906	
Respiratory comorbidity	Present: absent	14: 28	17: 31	26: 82	0.270	
Cardiovascular comorbidity	Present: absent	22: 20	24: 24	65: 43	0.429	
Tumor location	Ut: Mt: Lt: Ae	7: 17: 15: 3	5: 26: 16: 1	14: 59: 33: 2	0.520	
Clinical T	T1: T2: T3: T4	33: 2: 7: 0	35: 6: 7: 0	62: 16: 28: 2	0.157	
Clinical N	N0: N1: N2: N3	35: 4: 2: 1	38: 9: 0: 1	85: 17: 5: 1	0.650	
Clinical stage	I: II: III: IV	32: 5: 5: 0	34: 9: 2: 3	69: 23: 14: 2	0.200	
Preoperative treatment	None/NAC/NACRT	32: 10: 0	38: 10: 0	78: 24: 6	0.256	
Surgery						
Conduit	Stomach: colon	39: 3	47: 1	102: 6	0.516	
Dissection field	1: 2: 3	1: 19: 22	2: 14: 32	2: 36: 70	0.487	
Use of laparoscopy	Yes: no	34: 8	37: 11	86: 22	0.896	

Data are expressed as the number of cases or mean number \pm standard deviation

BMI body mass index, ASAPS American society of anesthesiologists physical status, NAC neoadjuvant chemotherapy, NACRT neoadjuvant chemoradiotherapy

 $^*p < 0.01, \#p < 0.05$

decreases respiratory secretion. It also improves the value of forced expiratory volume in 1 s (FEV₁), which contributes to reducing morbidities [30, 31]. In this study, short duration of smoking cessation before MIE highly correlated with postoperative morbidities. Although previous studies by Ferguson et al. and Mantziari et al. reported similar results [2, 6], those studies were mainly designed for OE. Thus, to the best of our knowledge, this is the first study to elucidate the importance of cessation in the prevention of postoperative complications in patients who have undergone MIE. For patients who continue smoking at their first visit of the preoperative evaluation, education in smoking cessation is considerably important, even in MIE. When we provide such information to patients before surgery, the current data is certainly helpful.

How long patients should maintain cessation before MIE to prevent postoperative morbidities is an interesting clinical issue. The current results suggested that smoking cessation ≥ 31 days is necessary to decrease severe morbidity and any pulmonary morbidity. For patients with

early-stage esophageal cancer, it is probably acceptable to delay surgery to allow the patient to quit smoking \geq 31 days. For patients with resectable advanced esophageal cancer, neoadjuvant therapy is commonly administered before MIE [32, 33]. NAC and NACRT require administration for 1 to 2 months before surgery. Thus, these patients can achieve sufficient duration of cessation \geq 31 days. On the other hand, although preoperative cessation > 91 days is considered desirable to reduce the likelihood of pneumonia after MIE, it may be difficult for all patients to achieve it. For patients who cannot sufficiently quit smoking, several precautions against postoperative pneumonia are important. Previous studies or meta-analyses have indicated that preoperative respiratory rehabilitation [34], preoperative oral care [35], perioperative administration of steroids [36, 37], and enforcing an enhanced recovery after surgery (ERAS) program [38] may be useful for preventing pulmonary morbidities.

Variables	Never-smoker	Duration of sm	P except never-		
	(n = 30)	\leq 30 days (<i>n</i> = 42)	31–90 days (<i>n</i> = 48)	\geq 91 days (<i>n</i> = 108)	smoker
Any morbidity of $CDc \ge II$	6 (20.0)	19 (45.2)	17 (35.4)	35 (32.4)	0.338
Severe morbidity of $CDc \ge IIIb$	3 (10.0)	13 (31.0)	4 (8.3)	10 (9.3)	0.001*
Pneumonia	2 (6.7)	9 (21.4)	8 (16.7)	6 (5.6)	0.011#
Any pulmonary morbidity	2 (6.7)	13 (31.0)	8 (16.7)	13 (12.0)	0.022#
Surgical site infection	4 (13.3)	5 (11.9)	5 (10.4)	6 (5.6)	0.349
Anastomotic leakage	1 (3.3)	8 (19.0)	6 (12.5)	15 (13.9)	0.645
Cardiovascular morbidity	3 (10.0)	3 (7.1)	4 (8.3)	5 (4.6)	0.634
In-hospital mortality	0	$1 (2.4)^{a}$	0	$1 (0.9)^{b}$	0.526
Hospital stay (days)	22 ± 4	25 ± 2	21 ± 2	24 ± 1	NS

Table 2 Short-term outcomes after esophagectomy according to the duration of smoking cessation

Data are expressed as the number of cases (%) or median number \pm standard error

CDc Clavien-Dindo classification, NS not significant

p < 0.01, # p < 0.05

^aDeath of respiratory failure

^bDeath of chronic myelomonocytic leukemia

Table 3 Factors associated with postoperative severe morbidity in patients with	a history of smoking
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Variables	Univariate		Multivariate ^a		
		HR (95% CI)	HR (95% CI) P		Р
Performance status	0	1 (referent)		1 (referent)	
	≥ 1	4.07 (1.106–15.01)	0.035	2.66 (0.661-10.737)	0.168
Smoking (Brinkman index)	Per 100 increase	1.07 (0.994-1.170)	0.071	1.06 (0.965-1.156)	0.236
Smoking cessation	\geq 31 days	1 (referent)		1 (referent)	
	\leq 30 days	4.55 (1.935-10.68)	< 0.001	4.89 (1.993-12.011)	< 0.001
Cardiovascular comorbidities	Absent	1 (referent)		1 (referent)	
	Present	2.51 (1.009-6.251)	0.048	2.58 (0.967-6.867)	0.058

^aAge at surgery (per 10 years), sex (male vs. female), Cooperative Oncology Group (ECOG) performance status (0 vs. \geq 1), body mass index (< 18.5 vs. \geq 18.5 kg/m²), past smoking [Brinkman index, year x number/day (number-years)], duration of smoking cessation, American society of anesthesiologists physical status (ASAPS) (1 vs. \geq 2), presence of diabetes mellitus, respiratory comorbidities, cardiovascular comorbidities, % volume capacity (VC) (< 80 vs. \geq 80%), forced expiratory volume (FEV) 1% (< 70 vs. \geq 70%), clinical T stage (T1, 2 vs. T3, 4), clinical N stage (N0 vs. N1–3), preoperative treatment (present vs. absent), operative time (per 60 min), intraoperative bleeding (per 100 g), and use of laparoscopy (yes vs. no)

HR hazard ratio, CI confidence interval

Several studies on surgical procedures may also be helpful, when MIE is performed on patients with insufficient cessation. Placing the patient in a prone position during MIE may contribute to reducing pulmonary morbidities, compared with morbidities associated with the left lateral position [39]. As for intraoperative ventilation technique, artificial pneumothorax with two-lung ventilation can abate lung injury, which may contribute to reducing pulmonary morbidity [40]. How we collect precise information on smoking status is another important issue. Based on the results of this study, a sufficient duration of smoking cessation preoperatively is integral to preventing morbidities after MIE. We commonly obtain information about duration of cessation via patients' self-reporting only. When patients report false information, we cannot objectively confirm it. We understand that it is important to establish a strategy to objectively determine whether patients have definitely stopped

Variables	Univariate		Multivariate ^a		
		HR (95% CI)	Р	HR (95% CI)	Р
Smoking (Brinkman index)	Per 100 increase	1.14 (1.042–1.240)	0.004	1.10 (1.001-1.209)	0.047
Smoking cessation	\geq 91 days	1 (referent)		1 (referent)	
	\leq 90 days	3.96 (1.489-10.53)	0.006	3.98 (1.442-10.971)	0.008
Cardiovascular comorbidity	Absent	1 (referent)		1 (referent)	
	Present	3.17 (1.128-8.931)	0.029	3.09 (1.037-9.186)	0.043

^aAge at surgery (per 10 years), sex (male vs. female), Cooperative Oncology Group (ECOG) performance status (0 vs. \geq 1), body mass index (< 18.5 vs. \geq 18.5 kg/m²), past smoking [Brinkman index, year x number/day (number-years)], duration of smoking cessation, American society of anesthesiologists physical status (ASAPS) (1 vs. \geq 2), presence of diabetes mellitus, respiratory comorbidities, cardiovascular comorbidities, % volume capacity (VC) (< 80 vs. \geq 80%), forced expiratory volume (FEV) 1% (< 70 vs. \geq 70%), clinical T stage (T1, 2 vs. T3, 4), clinical N stage (N0 vs. N1–3), preoperative treatment (present vs. absent), operative time (per 60 min), intraoperative bleeding (per 100 g), and use of laparoscopy (yes vs. no)

HR hazard ratio, CI confidence interval

Table 5 Factors associated with postoperative any pulmonary morbidity in patients with a history of smoking

Variables	Univariate		Multivariate ^a		
		HR (95% CI)	Р	HR (95% CI)	Р
Smoking (Brinkman index)	Per 100 increase	1.11 (1.029–1.198)	0.007	1.09 (1.009–1.183)	0.029
Smoking cessation	\geq 31 days	1 (referent)		1 (referent)	
	\leq 30 days	2.88 (1.295-6.411)	0.010	3.13 (1.351-7.252)	0.008
American society of anesthesiologists physical status	1	1 (referent)		1 (referent)	
	≥ 2	4.66 (1.067-20.37)	0.041	2.95 (0.584-14.889)	0.191
Cardiovascular comorbidity	Absent	1 (referent)		1 (referent)	
	Present	2.52 (1.108-5.728)	0.027	1.77 (0.698-4.466)	0.230

^aAge at surgery (per 10 years), sex (male vs. female), Cooperative Oncology Group (ECOG) performance status (0 vs. \geq 1), body mass index (< 18.5 vs. \geq 18.5 kg/m²), past smoking [Brinkman index, year x number/day (number-years)], duration of smoking cessation, American society of anesthesiologists physical status (ASAPS) (1 vs. \geq 2), presence of diabetes mellitus, respiratory comorbidities, cardiovascular comorbidities, % volume capacity (VC) (< 80 vs. \geq 80%), forced expiratory volume (FEV) 1% (< 70 vs. \geq 70%), clinical T stage (T1, 2 vs. T3, 4), clinical N stage (N0 vs. N1–3), preoperative treatment (present vs. absent), operative time (per 60 min), intraoperative bleeding (per 100 g), and use of laparoscopy (yes vs. no)

HR hazard ratio, CI confidence interval

smoking. Estimation of urinary nicotine and exhaled carbon monoxide are useful tests to check the current smoking status in patients. It would be important in the future to determine whether these tests can conclusively predict the occurrence of postoperative morbidities in MIE.

Potential limitations in this study are as follows. First, it was performed at a single institute and the sample size was insufficient. Second, as mentioned above, information about the duration of cessation was based on self-reporting, the truthfulness of which we could not objectively confirm.

In conclusion, smoking cessation is integral to the prevention of postoperative morbidities, even in MIE. Notably, short duration of smoking cessation ≤ 30 at the time of surgery correlated with high incidences of postoperative morbidities. Duration of cessation is desirable to be taken as long as possible to decrease postoperative morbidities. At least, preoperative cessation ≥ 31 days is preferable to decrease considerable morbidities. We believe the current results could contribute to encouraging patients preoperatively to quit smoking, thus reducing morbidities after MIE.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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