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ORIGINAL ARTICLE

Textbook outcome contributes to long-term prognosis in elderly patients with esophageal squamous cell carcinoma

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Abstract

Purpose: Textbook outcome (TO) is a composite quality measurement of outcomes for evaluating surgical procedures. We investigated whether TO can be used to predict outcomes after curative resection for esophageal squamous cell carcinoma (ESCC) in elderly patients.

Methods: We retrospectively analyzed 105 patients who underwent curative esophagectomy for ESCC from 2005 to 2020. In accordance with previous reports, TO consisted of 10 parameters. The patients were divided into two groups: those who achieved TO (TO) and those who failed to achieve TO (non-TO). We evaluated the association between TO and long-term survival.

Results: TO was achieved in 28 (26%) patients. The patients in the TO group were significantly older ($p = 0.02$). The parameter with the lowest achievement rate was "No hospital stay ≥21 days". The patients in non-TO group had significantly shorter overall survival than those in TO group ($p = 0.03$). Multivariable Cox regression analyses of overall survival revealed that lymph node metastasis (hazard ratio [HR], 3.42; 95% confidence interval [CI], 1.73–6.78; $p < 0.0002$) and non-TO (HR, 2.37; 95% CI, 1.05–5.65; $p = 0.03$) were significantly associated with poor overall survival.

Conclusion: TO can be used to predict outcomes after curative esophagectomy in elderly patients with ESCC.

KEYWORDS
elderly patient, esophageal cancer, textbook outcome

1 | INTRODUCTION

Esophageal cancer (EC) is the sixth leading cause of cancer-related death and the seventh most common cancer worldwide.[1,2] The incidence rate peaks between 60- and 69-years-old, and the number of elderly patients with EC is gradually increasing. About 40% of EC patients are over the age of 70, and the percentage is even higher in Japan at 47%.[3,4] For resectable EC, surgical resection is common. However, compared to other gastroenterological surgery, EC surgery carries a higher risk of postoperative morbidity and mortality.[5] Therefore, it is important to assess the risks associated with EC surgery in the elderly patients.

A systematic review on patient-related prognostic factors following esophagectomy revealed that age >70 years were associated with increased risk for mortality.[6] Other reports showed that nutritional index and performance status (PS) have been reported as poor prognostic factors in elderly EC patients.[7] However, there is controversy as to whether elderly EC patients who are about to undergo surgery can improve their nutritional and functional status and prognosis in a short period of time. Therefore, it is crucial to accurately determine prognosis in elderly EC patients in order to optimize and individualize treatment strategies.

Recently, a composite measure including all desirable outcomes called "textbook outcome (TO)" was developed from acute myocardial infarction, lung cancer, and gastrointestinal cancer surgery.[8–10] TO has been used to define achievement of multiple "ideal" or "optimal" surgical and postoperative quality measures from the patient's perspective. The advantage of this composite measure is that it provides a comprehensive indication of the quality of hospital care for patients and hospitals. Previous reports have shown that achieved TO was associated with better long-term outcome after esophagectomy for esophageal squamous cell carcinoma (ESCC).[11–14] However, the impact of TO on the long-term prognosis in elderly patients with ESCC remains unclear.

The current study aimed to investigate whether TO can be used to predict outcomes after curative ESCC surgery in elderly patients. To achieve this aim, we retrospectively analyzed data from 105 elderly patients who underwent esophagectomy for ESCC and then examined the relationship between TO and postoperative outcomes.

2 | MATERIALS AND METHODS

2.1 | Patients

From January 2005 to April 2020, 956 patients underwent esophagectomy for ESCC at the Department of Gastroenterological Surgery Kumamoto University Hospital. The inclusion criteria were as follows: (1) pathologically confirmed ESCC, (2) curative surgery at one-stage, (3) reconstructed by gastric tube, (4) aged 75 years or older. The exclusion criteria were as follows: (1) not SCC, (2) two-stage operation, (3) reconstructed by not gastric tube, (4) laryngo-esophagectomy, (5) combined resection of other organs, (6) salvage operation, (7) palliative esophagectomy for clinical stage IVb. Consequently, 105 patients were eligible.

This study was performed in accordance with the 1975 Declaration of Helsinki. The study procedures were approved by the institutional scientific review board of the Kumamoto University Hospital (#1909) and written informed consent was obtained from all patients.

2.2 | Textbook outcome definitions

In this study, textbook outcome includes 10 short-term surgical parameters which was defined by expert opinion within the scientific committee of the obligatory nationwide Dutch Upper GI Cancer Audit (DUCA) in 2017.[10]

Ten parameters are (1) complete resection according to the surgeon at the end of surgery, (2) tumor-negative resection margins (R0), (3) ≥15 lymph nodes retrieved and examined, (4) no intraoperative complication, (5) no complication of ≥ Clavien–Dindo (CD) grade II, (6) no reintervention ≤30 days after surgery, (7) no ICU readmission ≤30 days after surgery, (8) no hospital stay ≥21 days, (9) no in-hospital and no 30-day mortality, (10) no hospital readmission ≤30 days after discharge. Patients who achieved all of the above 10 parameters were classified as TO group, while other patients were classified as non-TO group. The patients' backgrounds and prognostic outcomes after surgery were retrospectively compared between the two groups using our prospectively maintained institutional clinical database. The rate of achievement of TO was also compared with cases under 75 years of age and examined by time period of surgical procedure.

2.3 | Treatment strategy and follow-up evaluation

The surgical procedures, pathological and final staging, adjuvant chemotherapy and postoperative surveillance were performed based on the recommendation of The Japanese Esophageal Society.[15–18] Staging was based on the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) grading system.[19] Intraoperative complications were defined based on Common Terminology Criteria for Adverse Events version 5.0 grade 3 or higher.

Postoperative complications and their grade were defined according to the Clavien–Dindo classification.[20] All patients were monitored for every 3–6 months until at least 3 years after treatment or until death. Overall survival (OS) was defined as the duration from the date of the operation to the date of death or last follow-up, with no restriction on the cause of death. Disease-free survival (DFS) was defined as the duration from the date of the operation to the date when sign of cancer is found or last follow-up. Cause-specific survival (CSS) was defined as the duration from the date of the operation to the date of death due to cancer or last follow-up.

2.4 | Statistical analysis

Statistical analyses were conducted using JMP version 16.0.0 (SAS Institute, Cary, NC, USA), and all statistical tests were two-sided at an α level of 0.05. The OS distributions were analyzed by the Kaplan–Meier method with the log-rank test. A Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable cox proportional hazards regression models were used to identify independent risk factors for OS. Variables included in the univariate logistic regression were known risk factors for postoperative morbidity and mortality. Variables included to multivariable cox proportional hazards

regression were selected after univariate logistic regression if the P value was less than 0.05. Categorical variables are presented as proportions, and non-normally distributed variables are presented as medians with interquartile ranges (25%–75%). Categorical data were compared using the chi-square test or Fisher's exact test, whereas non-normally distributed data were compared using the Kruskal–Wallis test.

3 | RESULTS

3.1 | Comparisons of patient characteristics

One hundred and five elderly patients were divided into the TO group ($n=28$, 26%) and the non-TO group ($n=77$, 74%) (Figure 1). The clinical characteristics of the 105 elderly patients after curative resection of ESCC are shown in Table 1. The mean age was 78 years (range, 75–89 years). The 105 patients included 85 (91%) men and 20 (19%) women. Age was significantly higher in the TO group than in the non-TO group (79 years vs. 77 years $p=0.016$), and there were no significant differences between the two groups for other characteristics.

3.2 | Comparisons of TO parameters

The number of achievements of each parameter of textbook outcome is shown in Figure 2. The parameters that most prevented patients from achieving TO was no hospital stay ≥21 days ($n=68$, 65%), followed by no complication of ≥ CD II ($n=35$, 33%). In order to examine the trends in TO achievement by age group, a comparison with the group under 75 years for each parameter is shown in Table 2. The achievement rate of TO in the group under 75 years was 31.5%, which was higher than in the over-75 group, although not statistically significant ($p=0.32$). Comparing each parameter separately, the achievement rates for no in-hospital and no 30-day mortality, and no reintervention ≤30 days after surgery were significantly lower in the elderly group ($p=0.0016$, 0.038).

In addition, considering the effects of minor changes in surgical techniques and treatment methods over a long period of this study, the achievement rate of TO by time period was examined (Table S1). There was no significant difference between the two groups in the achievement rate of TO and each parameter.

3.3 | Comparisons of long-term outcomes

The median follow-up was 28.2 months (range, 4.8–143 months). The Kaplan–Meier curves for OS and DFS in the TO and non-TO groups are shown in Figure 3A,B. OS and DFS were significantly longer in the TO than in the non-TO group ($p=0.033$, 0.037 by log-rank test). We also evaluated the survival analysis with CSS, which revealed that there was no difference between the two groups (Figure S1). While a significant difference was observed in OS between the TO and non-TO group, no clear difference was observed in CSS, leading us to focus on death from other causes in both groups (Table S2). Regarding the details of death from other causes, in the non-TO group, respiratory diseases, including pneumonia and respiratory failure, were significantly higher than in the TO group ($p=0.023$).

Univariable Cox regression analyses of OS revealed that ASA-PS≥1, neoadjuvant therapy (+), non-total minimally invasive esophagectomy (MIE), presence of lymph node metastasis, and non-TO were associated with poor OS ($p<0.05$) (Table 3). Subsequent multivariable Cox regression analyses of OS revealed that the presence of lymph node metastasis (HR, 3.08; 95% CI, 1.47–6.42; $p=0.002$) and non-TO (HR, 2.30; 95% CI, 1.03–5.59; $p=0.039$) were significantly associated with poor OS (Table 3). For the need for the 10 parameters of TO, we performed a survival analysis with the two parameters that had the poorest achievement rates; "No hospital stay ≥21 days", and "No complication of ≥ CD II", respectively. Although each Kaplan–Meier curves for non-TO group were similar to the Kaplan–Meier curves for TO group, there was no significant difference between each group (Figures S2 and S3). We also evaluated the survival analysis for achievement and non-achievement of

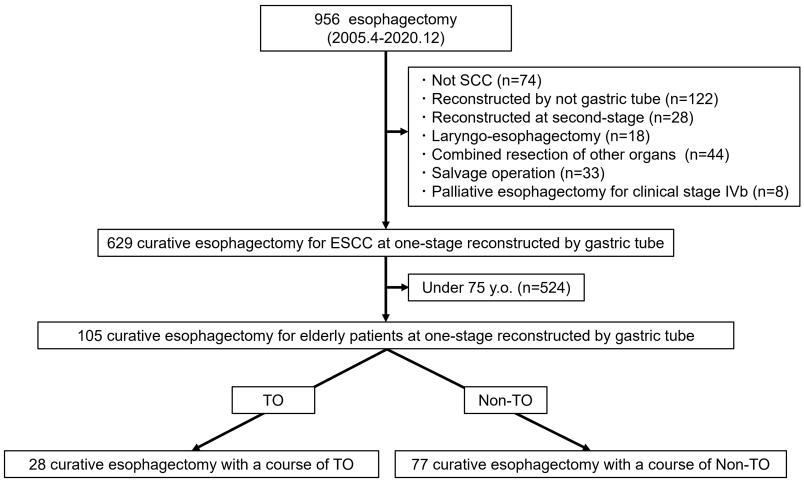

FIGURE 1 Flow chart of this study.

TO : Achieved Textbook Outcome Non-TO : Failured Textbook Outcome

TABLE 1 Patient characteristics of elderly patient cohort.

Characteristic	Total ($n=105$)	TO ($n=28$)	Non-TO ($n=77$)	p-Value
Age, years	78 (75–89)	79 (75–88)	77 (75–89)	0.016
Sex				
Male	85 (81)	23 (82)	62 (81)	0.85
Female	20 (19)	5 (18)	15 (19)	
ASA-PS				
0	75 (71)	20 (71)	55 (71)	0.89
1	28 (27)	8 (29)	20 (26)	
≧2	2 (2)	0 (0)	2 (3)	
Body mass index kg/m^2	21.6 (14–31)	21.7 (18–27)	21.5 (14–31)	0.67
Brinkman index				
<400	37 (35)	10 (36)	27 (35)	0.95
≧400	68 (65)	18 (64)	50 (65)	
Tumor depth				
pT1	36 (34)	11 (39)	25 (32)	0.45
pT2	18 (17)	4 (14)	14 (19)	
pT3	48 (46)	11 (39)	37 (48)	
pT4	3 (3)	2 (7)	1 (1)	
Lymph node metastasis				
pN0	60 (57)	17 (61)	43 (56)	0.43
pN1	28 (27)	8 (29)	20 (26)	
pN2	12 (11)	2 (7)	10 (13)	
pN3	5 (5)	1 (3)	4 (5)	
Neoadjuvant therapy				
Yes	66 (63)	21 (75)	45 (58)	0.11
No	39 (37)	7 (25)	32 (42)	
Surgical approach				
Non total MIE	66 (63)	16 (57)	50 (65)	0.46
Total MIE	39 (37)	12 (43)	27 (35)	
Lymph node dissection				
2 field	50 (48)	14 (50)	36 (47)	0.76
3 field	55 (52)	14 (50)	41 (53)	
Operation time (min)				
Median (range)	526 (272–765)	501 (272–757)	536 (326–765)	0.069
Blood loss (cc)				
Median (range)	419 (10–2851)	338 (10–1075)	448 (25–2851)	0.11

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; MIE, Minimal invasive esophagectomy; Non-TO, failure to achieve textbook outcome; TO, achieved textbook outcome.

"No hospital stay ≥21 days" and "No complication of ≥ CD grade II". There was no significant difference between the groups (Figure S4).

4 | DISCUSSION

This study investigated the association of TO after esophagectomy for elderly ESCC patients with long-term outcome. Achieved TO was associated with improved OS and DFS after esophagectomy and is an independent prognostic factor for OS. This study also found a significant difference in OS between the TO and non-TO groups without a clear difference in CSS, suggesting that deaths from other causes reflected the difference in OS between the groups.

As a characteristic of elderly ESCC patients, Sugita et al.[21] reported that while OS tends to be poorer, CSS does not significantly differ compared to younger patients, indicating a higher incidence of deaths from other causes. Actually, a high proportion of deaths from pneumonia and respiratory failure was observed in

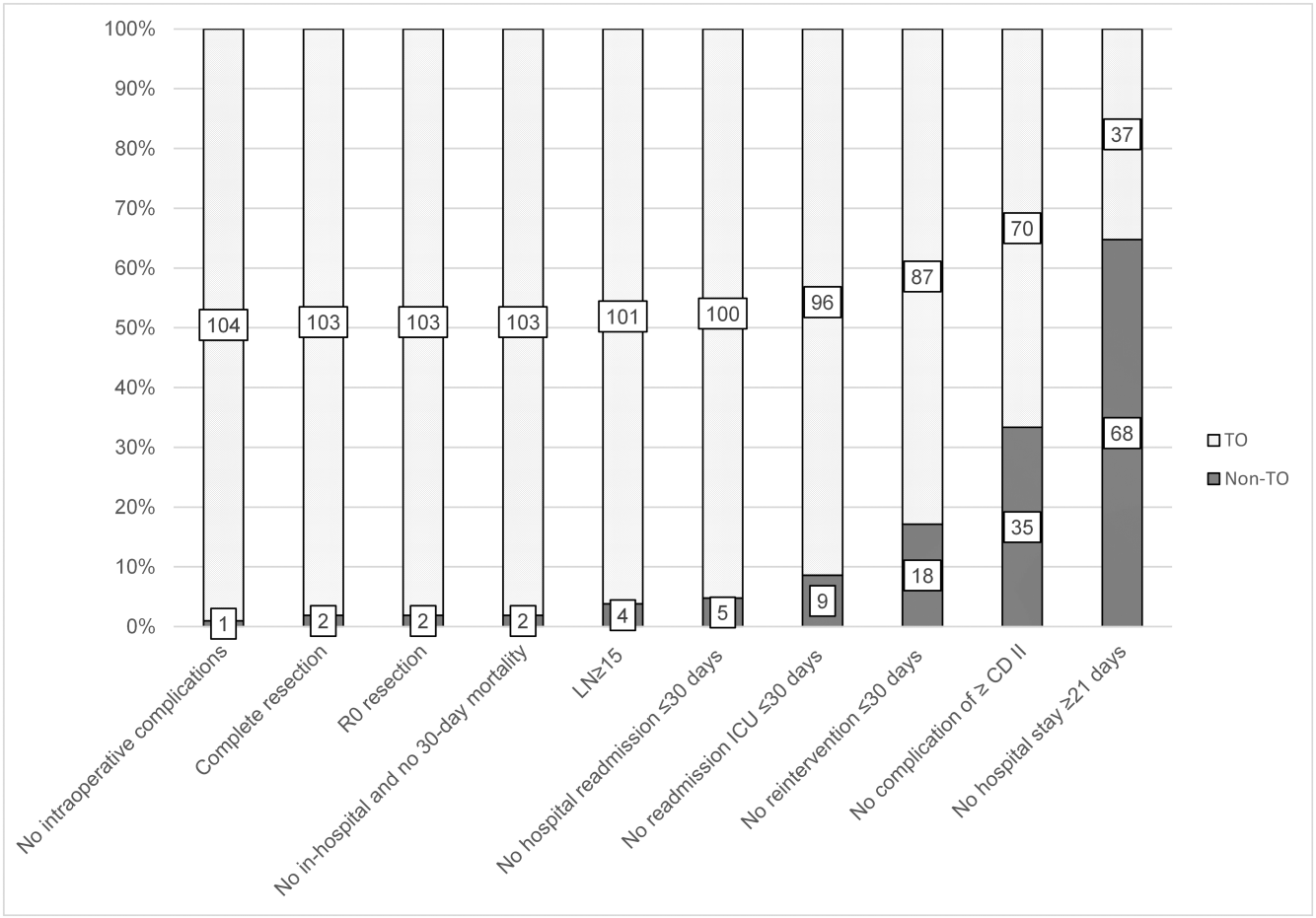

FIGURE 2 Proportion of patients achieving textbook outcome and each quality metric.

TABLE 2 The achievement rate for each parameter of TO by age group.

Parameter	All ($N = 629$)	Younger patients ($N = 524$)	Elderly patients ($N = 105$)	p-Value
TO	193 (30.6)	165 (31.5)	28 (26.7)	0.32
No intraoperative complications	617 (98.1)	513 (97.9)	104 (99.1)	0.43
Complete resection	599 (95.2)	496 (94.7)	103 (98.1)	0.13
R0 resection	599 (95.2)	496 (94.7)	103 (98.1)	0.13
No in-hospital and no 30-day mortality	627 (99.7)	524 (100)	103 (98.1)	0.0016
LN ≥ 15	608 (96.7)	507 (96.8)	101 (96.2)	0.77
No hospital readmission ≤30 days	595 (94.6)	495 (94.5)	100 (95.2)	0.74
No readmission ICU ≤30 days	596 (94.8)	500 (85.4)	96 (91.4)	0.094
No reintervention ≤30 days	558 (88.7)	471 (89.8)	87 (82.9)	0.038
No complication of ≥ CD II	396 (62.9)	326 (62.2)	70 (66.7)	0.37
No hospital stay ≥21 days	262 (41.7)	225 (42.9)	37 (35.2)	0.14

Abbreviations: CD; Clavian–Dindo; ICU, intensive care unit; LN, lymph node; TO, achieved textbook outcome.

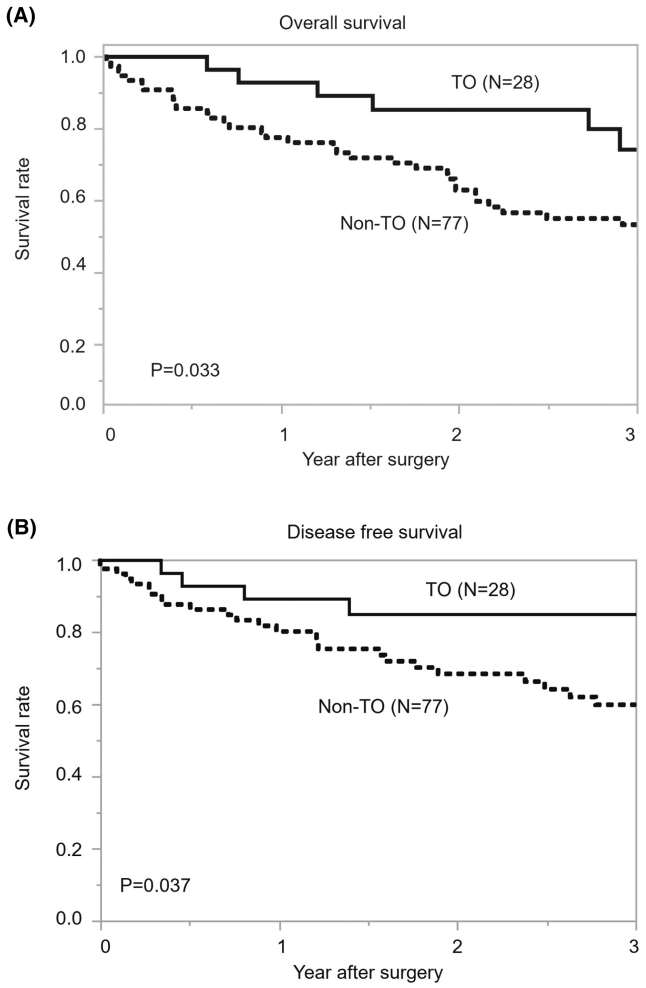

FIGURE 3 (A) Kaplan–Meier curves for overall survival after surgery according to the textbook outcome. (B) Kaplan–Meier curves for disease-free survival after surgery according to the textbook outcome.

the non-TO group. Our results suggests that TO may reflect the fatal physical functional decline in elderly patients with ESCC.

Aging is a major risk factor in esophagectomy. Yoshida et al.[22] reported that the risk of surgery-related mortality after esophagectomy increased as patients aged. Markar et al. reported that in-hospital mortality after esophagectomy was approximately twice as high for elderly patients as that of younger patients. In this study, in-hospital and 30-day mortality and reintervention ≤30 days was higher than that of younger patients. On the other hand, there was no significant difference between younger and elderly patients in terms of TO achievement. TO comprises 10 desired short-term quality-of-care parameters covering the complete surgical pathway from surgery to postoperative outcome. In-hospital and 30-day mortality and reintervention ≤30 days are also prognostic, but other factors of TO may influence prognosis.

"No complication of ≥ CD II" is the second parameter that prevented patients from achieving TO. Postoperative complications after esophagectomy have been reported to be associated with poor prognosis.[23] Postoperative complications after esophagectomy, resulting in prolonged hospital stay, predict lower long-term survival. One of the reasons that prolonged hospital stay poses a negative effect on prognosis might be insufficient postoperative treatment.[24] As an effort to prevent complications, Yoshida et al.[25] reported that preoperative smoking cessation ≥31 days is preferable to decrease severe morbidities of CD ≥ IIIb. A reduction in severe morbidity of CD ≥ IIIb may also indirectly contribute to a reduction in hospital stay, in-hospital and 30-day mortality, and readmission ICU ≤30 days.

The parameter that most strongly inhibited the achievement of TO in this study was "No hospital stay ≥21 days". In this study, elderly patients tended to have longer postoperative hospital stays than younger patients, regardless of the complications (Table S3). There have been various reports on the negative effects of prolonged hospitalization. Loyd et al.[26] reported that longer length of hospital stay

TABLE 3 Univariable and multivariable Cox regression analysis of overall survival.

		Univariable, HR (95% CI)	*p*-Value	Multivariable, HR (95% CI)	*p*-Value
Age	78 y.o.≦	1.57 (0.85–2.86)	0.13		
Sex	Male	1.21 (0.39–1.73)	0.62		
ASA-PS	≧1	2.08 (1.10–3.95)	0.029	1.59 (0.78–3.21)	0.19
Brinkman index	≧400	0.92 (0.49–1.71)	0.80		
Neoadjuvant therapy	(+)	1.92 (1.03–3.61)	0.043	1.01 (0.49–2.04)	0.97
LN dissection	2 field	0.87 (0.48–1.60)	0.67		
Surgical approach	Non-Total MIE	2.44 (1.13–5.28)	0.021	1.57 (0.65–3.77)	0.29
Operative time	526≦	1.06 (0.58–1.92)	0.84		
Blood loss	419≦	1.59 (0.87–2.89)	0.12		
Tumor depth	pT3≦	1.85 (0.98–3.48)	0.056		
Lymph node metastasis	Positive	3.42 (1.73–6.78)	0.0002	3.08 (1.47–6.42)	0.002
Time period	2005–2012	1.3 (0.71–2.38)	0.39		
Textbook outcome	Non-TO	2.37 (1.05–5.65)	0.032	2.30 (1.03–5.59)	0.039

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; LN, lymph node; MIE, Minimal invasive esophagectomy; Non-TO, failure to achieve textbook outcome.

is associated with greater likelihood of functional impairment in older patients. Ma et al.[24] reported that the level of physical performance after a prolonged hospital stay of esophagectomy may be so poor that postoperative treatment would be delayed, or even canceled. It is expected that comprehensive and intensive postoperative support, including enhanced recovery after surgery protocol, for elderly patients with EC leads to TO achievement. "No complication of ≥ CD grade II" and "No hospital stay ≥21 days" are not significant parameters to predict prognosis (Figures S2 and S3). TO comprises 10 desired short-term quality-of-care parameters covering the complete surgical pathway from surgery to postoperative outcome. Although TO is not a preoperative risk score that determines the indication for esophagectomy in elderly patients, TO is a useful predictor of the prognosis in elderly patients with ESCC because it can evaluate these perioperative parameters in a combined and comprehensive manner.

This study had some limitations. First, it was retrospectively designed, the patients were from only one institution, and the cohort was ethnically homogeneous. Because of the retrospective nature of the study and the long study period, the study contained several biases regarding perioperative management, minor surgical procedures. However, there was no effect of the time period on the rate of the achievement rate of TO. Second, the patients' backgrounds may have contained bias in terms of comorbidities. However, the present study elucidates the association between TO and poor prognosis, and we believe that TO may be a predictor of prognosis in elderly patients after curative resection for ESCC.

In conclusion, achieving TO was associated with a good prognosis after curative esophagectomy for elderly patients. Further multi-institutional studies with larger cohort are wanted to validate the present findings.

AUTHOR CONTRIBUTIONS

CM, CM managed the data collection. MI, CM, CM, AM, YM, TT, KK, YB, and NY performed the operations. MI, YB, NY, and HB supervised the management. CM and MI drafted the manuscript, and all authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Hideo Baba is a current Editorial Board Member of *AGSurg*.

ETHICS STATEMENT

Approval of the research protocol: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed Consent: Informed consent or substitute for it was obtained from all patients for being included in the study.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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