Impacts of complications after esophageal cancer surgery on health-related quality of life and nutritional status

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Abstract
Background The long-term impacts of post-operative complications, especially pulmonary complications and anastomotic leakage, on health-related quality of life (HRQoL), nutritional status and body composition remain to be fully addressed in patients undergoing esophageal cancer surgery.

Methods Patients who underwent esophagectomy between 2015 and 2019 and survived without recurrence were eligible. HRQoL (European Organization for Research and Treatment of Cancer QLQ-C30 and the QLQ-OES18 questionnaires), nutritional and body composition data were prospectively evaluated before and at 3, 6, 12 and 24 months after surgery. Collected data were compared between patients with post-operative complications and those without.

Results In total, 88 patients were included. Overall complications, anastomotic leakage and pulmonary complications developed in 48 (54.5%), 20 (20.7%) and 18 (20.5%) patients, respectively. Patients with pulmonary complications had significantly more reflux-related symptoms (dry mouth; $P = 0.03$, coughing; $P = 0.047$), and more difficulties with eating at 24 months after surgery, as compared to those without such complications. Anastomotic leakage increased pain, speaking problems and dysphagia up to 6 months after surgery. Patients with pulmonary complications had significantly lower prealbumin levels ($P = 0.01$, 0.02 and 0.008 at 6, 12 and 24 months after surgery, respectively) and lower prognostic nutritional index values over time after surgery than those without these complications. In contrast, anastomotic leakage was not associated with poor nutritional status post-operatively. Body composition was not affected by the occurrence of complications.

Conclusion Patients who developed post-operative complications, especially pulmonary complications, had long-lasting negative HRQoL outcomes and poor nutritional status after esophagectomy.

Keywords Esophageal carcinoma · Health-related quality of life · Nutritional status · Post-operative complications

Introduction
Esophageal carcinoma (EC) remains a major cause of cancer-related mortality worldwide [1]. Curative treatment for EC usually involves esophagectomy with pre- or post-operative chemotherapy and/or radiotherapy [2]. Many patients undergoing esophagectomy experience considerable deterioration in health-related quality of life (HRQoL) even after surviving refractory disease [3].

Previous studies have identified several factors related to post-operative HRQoL; surgical approaches [4, 5],
pre-operative comorbidities [6] and post-operative complications [7, 8]. Less invasive surgical approaches, such as minimally invasive esophagectomy (MIE) and robot-assisted esophagectomy (RAMIE), reportedly reduce pain-related problems; however, problems including reflux, coughing and eating difficulties have proven resistant to innovations in surgical approaches [4, 5].

Esophagectomy is still associated with considerable morbidity [9]. The negative survival impacts of post-operative complications have been elucidated in patients undergoing surgery for EC [10]. Furthermore, prior studies have revealed post-operative complications to result in deterioration of HRQoL after esophagectomy [7, 8]. The time-course effects of specific complications on HRQoL, nutritional status and body composition, have yet to be addressed taking the tumor entity into consideration.

This study aimed to elucidate the long-term effects of two major post-operative complications after esophagectomy: pulmonary complications and anastomotic leakage. We conducted a longitudinal survey to evaluate their impacts on long-term changes in well-validated HRQoL scores, nutritional status and body composition.

Materials and methods

Patients

Between April 2015 and March 2019, a total of 229 patients with pathologically confirmed EC underwent potentially curative esophagectomy at the University of Tokyo Hospital. Patients undergoing salvage surgery (n = 28), those receiving two-stage operations (n = 14), those having synchronous multiple malignancies (n = 16), the very elderly (age > 85) (n = 5) and patients who did not consent to participate in the survey (n = 28) were excluded. Patients who underwent transthoracic esophagectomy (n = 15) were also excluded since this procedure without thoracotomy was applied only to high-risk patients in our institution. The remaining 123 patients were prospectively surveyed, and among them 88 long-term survivors without recurrence within 2 years after surgery were analyzed. The Charlson comorbidity index (CCI) [11] was used to assess patient frailty at the time of surgery. This prospective study was approved by the local ethics committee of the faculty of medicine at the University of Tokyo (UMIN ID: 000,017,565).

Perioperative management and surgical treatment

Cisplatin (CDDP) plus 5-fluorouracil (5-FU) (CF) administration was the standard pre-operative treatment and a regimen consisting of three drugs (CDDP, 5-FU, and docetaxel; DCF therapy) was optional. Robot-assisted transmediastinal esophagectomy, or TME, with three-field lymphadenectomy was performed using a robotic surgical system, da Vinci S or Xi (Intuitive Surgical, Sunnyvale, CA, USA) [4]. Our standard TTE procedures consisted of subtotal esophagectomy with mediastinal lymphadenectomy via right thoracotomy, upper abdominal lymphadenectomy and reconstruction with intrathoracic anastomosis using a gastric tube. During the study period, TME was generally employed for cT1-2N0-1 cases. The 7th Edition of the TNM classification [12] was applied to stage the tumors.

Definition of complications

Post-operative complications were defined as adverse events occurring within 30 days of surgery or during the in-hospital period, and severities were assessed using the Clavien–Dindo (C–D) classification [13]. Patients with Grade II or higher severity were regarded as having complications. Each complication was categorized according to the international consensus [14].

Pulmonary complications were defined as the presence of one or more of the following post-operative conditions [10]: initial ventilatory support for more than 48 h, intubation for respiratory failure, acute respiratory distress syndrome, pneumonia, pleural effusion and atelectasis requiring bronchoscopy or antibiotics. Anastomotic leakage was defined as clinical signs of leaking, such as erythema, skin edema, emission of fluid or pus from a surgical wound or cervical drain or a radiographically detected leak confirmed by esophagography and/or computed tomography [15].

Data collection

Written HRQoL questionnaire responses were collected at the time of admission for surgery and at 3, 6, 12 and 24 months after surgery, according to a recent study [5]. HRQoL was measured using well-established questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [16] and EORTC QLQ-OES18 [17]. Higher scores correspond to better HRQoL in the function scales and the global QOL scale, whereas higher scores for symptom scales and single items represent more problems. The nutritional status (albumin and prealbumin) and body composition data were obtained on the same schedule. Body composition was measured by bioelectrical impedance analysis using an Inbody 770 machine (Biospace, Tokyo, Japan).

Statistical analysis

The QOL data obtained in past investigations were presented as means and standard errors [18]. In this study, the $\chi^2$ test and Fisher’s exact test were used for categorical data.
The 2 groups were compared using the t test for independent samples if the data were normally distributed and the Mann–Whitney U test if the data distribution was not normal. Statistical analyses were carried out using JMP 13.0.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

Among the 123 patients, 22 (17.9%) developed recurrence within 2 years of esophagectomy. One patient (0.8%) died due to pneumonia at 18 months after surgery and 12 (9.8%) did not return the questionnaires. The remaining 88 (71.5%) patients, who survived for at least 2 years after surgery without recurrence, were eligible for inclusion in the analysis. The clinicopathological features of these 88 patients are presented in (Table 1). Fifty-eight (65.9%) patients underwent TME. There were 37 (42.0%), 25 (28.4%), 23 (26.2%) and 3 (3.4%) patients with pStage 0–I, II, III and IV disease, respectively. High lymph node yield was achieved in our series.

Post-operative complications

The details of the post-operative complications are shown in (Table 2). Overall complications (≥ Grade II according to C–D classification) developed in 48 (54.5%) patients. The most common post-operative complications were anastomotic leakage, which occurred in 20 of the 88 patients (20.7%), pulmonary complications in 18 (20.5%) and recurrent nerve palsy in 8 (9.1%). Patient characteristics according to the presence of each complication are described in Supplementary Table 1. There were no remarkable differences between patients with and those without complications.

Time-course changes in HRQoL scores

Time-course changes in problems related to reflux and coughing (reflux, dry mouth, difficulty with coughing and

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Table 1 Characteristics of 88 patients included in the analysis

| Variables                        | No. of patients (%) |
|----------------------------------|---------------------|
| Age, y Median (range)            | 67 (43–82)          |
| Sex                              |                     |
| Male                             | 63 (71.6)           |
| Female                           | 25 (28.4)           |
| Comorbidity (CCI ≥ 2)            | 8 (9.1)             |
| Tumor location                   |                     |
| Lt                               | 29 (33.0)           |
| Mt                               | 51 (57.9)           |
| Ut                               | 8 (9.1)             |
| Neoadjuvant chemotherapy         | 32 (36.4)           |
| Surgery                          |                     |
| TTE                              | 83 (94.3)           |
| TME                              | 58 (65.9)           |
| Tissue Type                      |                     |
| SCC                              | 83 (94.3)           |
| AC                               | 5 (5.7)             |
| PSStaging                        |                     |
| PSStage 0–I                      | 37 (42.0)           |
| PSStage II                       | 25 (28.4)           |
| PSStage III                      | 23 (26.2)           |
| PSStage IV                       | 3 (3.4)             |
| Lymphadenectomy                  |                     |
| 2 fields                         | 13 (14.8)           |
| 3 fields                         | 75 (85.2)           |
| No. of retrieved lymph nodes, Median (range) | 64 (9–158) |
| Curability, R1-2                 | 3 (3.4)             |

CCI: Charlson comorbidity index, TTE: transthoracic esophagectomy, TME: transmediastinal esophagectomy, SCC: squamous cell carcinoma, AC: adenocarcinoma

Table 2 Postoperative complications occurring within 30 days of esophageal cancer surgery in our cohort

| Variables                        | No. of patients (%) |
|----------------------------------|---------------------|
| Overall complications (≥ Grade II) |                     |
| No                               | 40 (45.5)           |
| Yes                              | 48 (54.5)           |
| Medical complications*           |                     |
| Pulmonary complications           | 18 (20.5)           |
| Pneumonia                        | 11 (12.5)           |
| Acute respiratory disease syndrome| 4 (4.5)             |
| Pleural effusion                 | 1 (1.1)             |
| Reintubation                     | 1 (1.1)             |
| Initial ventilatory support for more than 48 h | 1 (1.1) |
| Cardiovascular                   |                     |
| Atrial fibrillation              | 3 (3.4)             |
| Deep vein thrombosis             | 1 (1.1)             |
| Acute heart failure              | 1 (1.1)             |
| Others                           |                     |
| Delirium                         | 1 (1.1)             |
| Urinary tract infection          | 2 (2.3)             |
| Surgical complications*          |                     |
| Anastomotic leakage              | 20 (22.7)           |
| Recurrent nerve palsy            | 8 (9.1)             |
| Surgical site infection          | 3 (3.4)             |
| Chylothorax                      | 2 (2.3)             |

*Some patients had more than one type of complication
†Clavien–Dindo classification
taste abnormalities), symptoms related to eating (nausea/vomiting, appetite loss, eating difficulties and dysphagia) and pain-related symptoms (pain, fatigue, dyspnea and insomnia) are shown in (Figs. 1, 2, 3), respectively. Overall complications had no significant impacts on either symptoms or single items.

Notably, patients with pulmonary complications had more problems related to reflux and coughing than those

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**Fig. 1** Time-course changes in symptoms related to reflux and coughing. Mean scores for A reflux, B dry mouth, C excessive coughing, and D altered taste in patients with (●) and without (○) complications were calculated based on QLQ-OES18 questionnaire responses. Error bars represent standard errors. Student’s t test was used to determine the statistical significance of differences (*P < 0.05).
without pulmonary complications (Fig. 1); reflux ($P = 0.1$ at 24 months), dry mouth ($P = 0.02$ at 12 months and $P = 0.03$ at 24 months) and coughing ($P = 0.047$ at 24 months). Pulmonary complications also exacerbated some of the symptoms related to eating (nausea/vomiting and eating difficulties) at 24 months after surgery, although the differences did not reach statistical significance ($P = 0.051$ and 0.06, respectively, Fig. 2). Pain-related symptoms did

Fig. 2 Longitudinal changes in symptoms related to eating. Mean scores for A nausea/vomiting, B appetite loss, C eating difficulties, and D dysphagia in patients with (●) and without (○) complications were calculated based on QLQ-OES18 questionnaire responses. Error bars represent standard errors. Student’s t test was used to determine the statistical significance of differences (*$P < 0.05$)
not differ between the two groups, except for insomnia at 24 months after surgery (Fig. 3). Anastomotic leakage was associated with significantly poorer scores for pain, trouble speaking and dysphagia at 12 months after surgery, although the differences had disappeared by 24 months after surgery (Fig. 3). In contrast, post-operative complications had a modest impact on global QOL and functional scales within 2 years after surgery, as presented in Supplementary Table 2.

Fig. 3 Time-course changes in pain-related symptoms. Scores for A pain, B fatigue, C dyspnea, and D insomnia were compared between patients with and without overall complications (left), pulmonary complications (middle), and anastomotic leakage (right). Error bars represent standard errors. Student’s t test was used to determine the statistical significance of differences (* P < 0.05)
Longitudinal changes in body composition data and nutritional status

Figure 4 shows time-course changes in nutritional parameters. Patients with pulmonary complications had significantly lower prealbumin at 3, 6, 12 and 24 months after surgery than those without these complications ($P = 0.049$, 0.01, 0.02 and 0.008, respectively, Fig. 4). Multivariate analysis revealed the occurrence of pulmonary complications to be independently associated with low prealbumin at 2 years after surgery (Supplementary Table 3). The presence of pulmonary complications also decreased PNI at 12 and 24 months after surgery, although the differences did not reach statistical significance ($P = 0.058$ and 0.09, respectively, Fig. 4). In contrast, the presence of overall complications and anastomotic leakage did not significantly change nutritional status. There was no influence of complications on the body composition data (Supplementary Table 4).

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**Fig. 4** Longitudinal changes in nutritional status. Nutritional markers (A: albumin, B: prealbumin, C: PNI) were measured before and after surgery up to 2 years, and were compared between patients with and without overall complications (left), pulmonary complications (middle), and anastomotic leakage (right). Error bars represent standard errors. Student’s $t$ test was used to determine the statistical significance of differences ($*P < 0.05$, $**P < 0.01$)
Discussion

This study revealed complications after esophageal cancer surgery, especially pulmonary complications, to be associated with long-term negative HRQoL outcomes and poor nutritional status. Pulmonary complications were associated with increases in problems related to reflux/coughing and eating, while not worsening pain-related symptoms. Notably, patients with pulmonary complications had long-lasting poor nutritional status.

Esophagectomy is still associated with considerable morbidity; the overall incidence of complications is reportedly approximately 60% [9]. These complications must be managed very carefully to prevent early post-operative mortality [15]. Importantly, with an increasing number of long-term survivors after curative resection for EC, the long-term impacts of post-operative complications have recently been highlighted [19].

Generally, the HRQoL of patients undergoing esophagectomy markedly deteriorates immediately after surgery, but then gradually recovers to a nearly pre-operative level within 3–5 years after surgery; however, some patients do not experience restored HRQoL after surgery, experiencing multiple concurrent long-lasting symptoms, such as reflux and eating problems [20]. Recent findings suggested minimally invasive surgical approaches to reduce reflux problems [4, 18], but an abundance of evidence has shown that symptoms associated with eating, reflux and coughing are refractory and difficult to ameliorate with surgical modifications [5]. Rather, post-operative complications reportedly exert long-lasting negative effects on HRQoL outcomes including eating problems [7, 8].

The influences of post-operative complications on long-term HRQoL have already been investigated [7, 8]. However, the cohorts in prior studies were mainly comprised of patients with adenocarcinoma and details of the surgical procedures were not reported. Furthermore, the time-course effects of specific complications on HRQoL, nutritional status and body composition, were not addressed in earlier studies. As such, the strengths of this study included its longitudinal design, evaluating a variety of physiological status parameters (HRQoL, nutritional status and body composition) and employing a cohort comprised mainly of ESCC patients who underwent radical esophagectomy with extended LN dissection involving high LN yield.

In our study, overall complications had modest impacts on HRQoL outcomes. Therefore, to further dissect the effects of each individual complication, we focused on two major complications and investigated their individual impacts. Notably, the impacts of pulmonary complications on HRQoL and nutritional status differed from those of anastomotic leakage. Patients with anastomotic leakage had more pain, speaking and dysphagia problems at 6 months after surgery, although these negative effects had diminished at 2 years post-operatively, a finding in agreement with those of previous studies [8].

Pulmonary complications exerted negative impacts on several aspects of HRQoL over time. Most notably, pulmonary complications were associated with more dry mouth, coughing and reflux, all of which correlate highly with each other [21], at a later time after esophagectomy. These symptoms reportedly cause insomnia [19], which might explain the observation that patients with pulmonary complications had significantly worse insomnia at 2 years after surgery than those without such complications. Furthermore, patients with pulmonary complications had more symptoms of nausea/vomiting and eating difficulties than those without these complications at 2 years after surgery, although the differences were not statistically significant.

The presence of pulmonary complications was significantly associated with poor nutritional status. In this study, we employed various nutritional indices including albumin, PNI and prealbumin. Of note, prealbumin reportedly reflects nutritional status more clearly than other nutritional parameters and is, thus, useful for evaluating the benefits of nutritional support [22]. As such, our findings accurately reflect nutritional status over time after surgery. These observations raise the possibility that pulmonary complications led to an increase in reflux, coughing and eating difficulties, resulting in malnutrition [23].

The mechanisms underlying the different impacts of pulmonary complications and anastomotic leakage on post-operative nutritional status are not fully understood. A recent study revealed post-operative HRQoL to improve more rapidly in patients with surgical complications than in those with medical complications [8]. Furthermore, prior studies have suggested pulmonary complications to worsen the patient’s general medical condition, resulting in high non-cancer mortality [10] [24]. These observations, together with our findings, suggest that pulmonary complications result in prolonged poor patient physical status, though further studies are necessary to validate our findings and elucidate mechanisms by which pulmonary complications alone impair poor nutritional status over time after surgery.

On the other hand, previous studies have suggested that eating problems contributed to post-operative malnutrition, whereas dysphagia and reflux did not [25]. Although nutritional status appears to be a good indicator when estimating HRQoL, the relationship between each HRQoL measure and nutritional status has yet to be fully addressed [26]. We also evaluated body composition data, but detected no significant differences according to whether or not post-operative complications developed.
Poor HRQoL at 6 months after esophageal cancer surgery is reportedly associated with increased mortality risk [27]. Patients with post-operative complications, especially pulmonary complications, reportedly had poor survival outcomes [10]. Notably, the negative survival impact of pulmonary complications is not due to an increase in cancer-related death, but rather mainly to more non-cancer deaths [15]. Our observations, together with those of a recent study [10], indicate that pulmonary complications potentially worsen a patient’s general medical conditions, resulting in increased all-cause mortality.

Our study has limitations. First, it was a single-institution study. It seems likely that a multi-center collaborative study with a large cohort could achieve more convincing results. Limitations include that this was a nonrandomized comparison study and, therefore, the observed differences in HRQOL may reflect other clinical variables that were not adjusted for. Second, the small patient number has limited statistical power. Additionally, the sample size of long-term survivors was further limited due to the poor long-term outcomes of EC patients. Third, we did not evaluate the associations between the severity of the complications and HRQoL outcomes, a topic which merits further detailed examination in future studies. Fourth, we followed HRQoL data only up to 2 years after surgery and do not have long-term follow-up data on the HRQoL of patients. While EC patients who underwent Ivor Lewis esophagectomy and survived for 2 years without recurrence had relatively good HRQoL outcomes, comparable to those of a healthy reference population [20], assessing the very long-term HRQoL outcomes (≥5 years post-operatively) is also crucial for patients undergoing esophagectomy [8]. Lastly, we evaluated the impacts of pulmonary complications and anastomotic leakage separately, but some patients had both of these complications since medical complications often lead to surgical complications and vice versa. This potential mixed cause–effect pattern must be taken into consideration when interpreting the results.

In conclusion, our findings suggest patients who developed post-operative complications, especially pulmonary complication, to have poor HRQoL and nutritional outcomes over time after esophagectomy. Our results are anticipated to help clinicians take measures to prevent complications and optimize post-operative long-term strategies, thereby improving the HRQoL of patients.

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