Prognostic Factors and Causes of Death in Patients Cured of Esophageal Cancer

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SYNOPSIS

The negative prognostic factors identified in cured esophageal cancer patients were age, being male, pulmonary comorbidities, synchronous cancers, colonic/jejunal interposition, blood transfusion, pulmonary complications, and adjuvant radiotherapy, with pulmonary diseases and other cancers being the most common causes of death.

ABSTRACT

Background: The number of patients cured of esophageal cancer after esophagectomy is gradually increasing owning to advances in surgical techniques, perioperative management, and adjuvant therapies. This study assessed the clinical course and sought to identify the prognostic factors of these patients.

Methods: A series of 220 consecutive patients who underwent esophagectomy and survived for more than 5 years with no relapse were enrolled. Survival analysis was performed using 25 variables including patient characteristics and operative and perioperative factors. Potential prognostic factors were identified by univariate and multivariate analyses, and the development of other primary cancers and the causes of death were retrospectively reviewed.

Results: The overall 10-, 15-, and 20-year survival rates were 71.6, 50.1, and 32.2%, respectively, with a median survival time of 180 months (range, 61–315 months). The negative independent prognostic factors identified were age at surgery (hazard ratio [HR], 1.05; $P < 0.01$), being male (HR, 2.62; $P = 0.02$), pulmonary comorbidities (HR, 2.03; $P = 0.02$), synchronous presence of other cancers (HR, 2.35; $P < 0.01$), colonic/jejunal interposition (HR, 1.76; $P = 0.03$), perioperative blood transfusion (HR, 1.92; $P = 0.02$), development of pulmonary complications (HR, 1.71; $P = 0.02$), and adjuvant radiotherapy (HR, 2.13; $P = 0.01$). Pulmonary diseases and other primary cancers were found to be the most common causes of death.

Conclusions: Careful follow up including the surveillance of other primary cancers is required for long-term survivors of esophageal cancer after esophagectomy.

INTRODUCTION

Esophageal cancer is one of the most lethal malignancies, and esophagectomy with lymph node dissection is the mainstay of treatment for locally advanced cancer. Owing to advances in this procedure, perioperative management, and adjuvant therapies such as chemoradiotherapy (CRT), prognosis is steadily improving, with a recently reported 5-year overall survival rate of 44.1%. [1] In addition, the number of patients who are considered to be cured of the disease is gradually increasing. However, a lack of follow-up or referrals to general practitioners thereafter means their clinical course is not being fully investigated.

Esophagectomy is a highly invasive procedure that is associated with a considerable risk of serious complications, especially in patients with severe comorbidities or in the elderly population. [2-5] Patients who survive the perioperative period may be at risk of not only cancer recurrence, but also various disease states such as malnutrition and pneumonia. Furthermore, adjuvant therapy might worsen the patient's general condition (e.g., developing a secondary cancer or an immunocompromised state) and may have a negative impact on long-term outcomes. [6-9] Such risks might prevail for more than 5 years and are therefore important prognostic factors in cured esophageal cancer patients who are no longer affected by the cancer itself. Identifying these factors is critical for establishing better management and improving the survival and quality of life of such patients. This study assessed the clinical course with the aim of identifying the prognostic factors for long-term survival after esophagectomy for cancer.

METHODS

Patients

A series of 606 consecutive patients underwent esophagectomy for esophageal cancer at Niigata University Medical and Dental Hospital between January 1985 and December 2005. Of them, 254 patients (41.9%) survived for more than 5 years. We excluded 34 patients who had cancer recurrence within 5 years after esophagectomy. This left 220 patients (36.3%) defined as cured esophageal cancer patients (i.e., survived for more than 5 years after surgery with no recurrent disease) for analysis because there was no patient with recurrent disease thereafter. Their clinicopathological characteristics, perioperative factors, and follow-up data including causes of death were reviewed from prospectively collected data.

Comorbidities and other cancers

Comorbidities were assessed before surgery on the basis of medical history, current presentation, and findings on chest X-ray, electrocardiography, arterial blood gas analysis, and pulmonary function, biochemical, and hematological tests, as previously described with some modifications. [3] In brief, comorbidities were defined as follows: past or current symptoms and signs of pulmonary diseases or abnormal pulmonary function [forced expiratory volume at 1 second (FEV 1) of <60% or arterial oxygen tension <70 mmHg], cardiovascular disease or abnormal electrocardiography, renal disease or 24-h creatinine clearance <70 ml/min, or cerebrovascular disease; established diagnosis of diabetes mellitus; and other abnormal organ functions requiring medical intervention. The physical status classification system established by the American Society of Anesthesiologists was used to evaluate general preoperative risk.

Synchronous cancers were defined as those occurring within 2 months of esophageal cancer, while metachronous cancers were defined as those occurring more than 2 months before or after esophageal cancer. [10]

Staging and surgical procedures

Tumor staging was based on the tumor-node-metastasis (TNM) classification defined by the Union for International Cancer Control (UICC). [11] Surgical procedures, including the approach and the extent of lymphadenectomy, depended mainly on tumor location, preoperative staging, and intraoperative findings, as described elsewhere. [12] In brief, transthoracic esophagectomy with extended mediastinal lymphadenectomy was performed for carcinoma of the upper or middle thoracic esophagus regardless of nodal status, and for the lower thoracic esophagus with mediastinal lymph node metastasis based on clinical staging. Transhiatal esophagectomy with limited mediastinal lymphadenectomy was performed for carcinoma of the lower thoracic esophagus without mediastinal lymph node metastasis based on clinical staging. [12] Three-field lymphadenectomy was indicated for patients younger than 75 years of age without severe comorbidities. Gastric tube placement was the first choice for reconstruction and colonic/jejunal interposition was selected when the patient had existing gastric cancer or had previously undergone gastrectomy. Cervical anastomosis was performed in all patients.

Adjuvant therapy

During the study period, various adjuvant therapies were performed before or after esophagectomy. Postoperative chemotherapy with oral fluoropyrimidine was selected

for cases treated in the mid-1980s [13, 14], followed by cisplatin plus 5-fluorouracil as the standard adjuvant therapy for cases treated in the early 1990s [15]. A randomized trial comparing postoperative versus preoperative chemotherapy was subsequently conducted in the early 2000s, [16] and some patients who participated in the trial were included in this study.

Postoperative complications

Postoperative complications were defined as grade II or more severe according to the Clavien-Dindo classification. [17] Pulmonary complications included acute respiratory failure, pneumonia, pleural effusion, pleural empyema, and chylothorax. Recurrent laryngeal nerve palsy (RLNP) was diagnosed based on clinical presentations and assessed by laryngofiberscopy from 1994 in all patients regardless of the presence of hoarseness.

Follow-up

All patients were periodically followed up at our institution or affiliated hospitals for at least 5 years after esophagectomy. Some of the patients stopped their regular outpatient visits and were referred to general practitioners. Eventually, all but 2 patients were followed until their death or until December 2011. Two patients could not be followed up at 106 and 180 months after esophagectomy and were treated as censored cases. Body weight (BW) was recorded immediately before surgery and at each outpatient visit. The BW reduction rate was calculated using BW 5 years after surgery and BW before surgery.

Statistical analysis

The potential prognostic factors assessed in this analysis included patient and characteristics, intra- and perioperative variables listed in Table 1 and 2. Reciprocal correlations were assessed using the Chi-squared test for categorical variables or the Mann-Whitney U test for continuous variables. Survival rate was calculated from the date of surgery until death or the last follow up for surviving patients by the Kaplan-Meier method. The significance of the differences between survival curves was assessed using the log-rank test. Factors with a *P* value of less than 0.1 in univariate analysis were entered into multivariate analysis using Cox's proportional hazards regression model. Continuous variables including age at surgery, BW, and number of lymph nodes removed were also entered into the multivariate model. A *P* value of less than 0.05 was considered statistically significant. All data were analyzed using StatView for Windows version 5.0 (SAS Institute, Inc., Cary, NC).

RESULTS

Clinicopathological characteristics

The characteristics and perioperative factors of the 220 patients are summarized in Table 1. Seventy-two patients (32.7%) had one or more comorbidities, and 106 patients (48.2%) developed at least one complication. Abnormal FEV 1 was the most common pulmonary comorbidity (14 patients, 66.7%). Chemotherapy, radiotherapy, and CRT were performed preoperatively in 5, 1, and 2 patients, respectively; while postoperatively in 65, 4, and 13 patients, respectively. The remaining 131 patients received no adjuvant therapy.

The median number of lymph nodes removed during surgery was 43 (range, 2–147). No significant differences were noted in the number removed between patients with pulmonary comorbidities and those without (median, 44 vs. 43, $P = 0.73$). However, significantly more lymph nodes were removed in patients with pulmonary complications than in those without (median, 55.0 vs. 33.5, $P < 0.01$).

Other primary cancers

Ninety-six patients (43.6%) had other primary cancers, and of them, 19 (19.8%) had other primary cancers in 2 or more organs excluding the esophagus. The stomach was the most affected organ, followed by the head and neck region and the lung. Gastric cancer was found before esophagectomy in 9 patients, at the time of esophagectomy in 17, and after esophagectomy in 22. Twenty-five patients (11.4%) had metachronous cancers before esophagectomy, 23 (10.5%) had synchronous cancers, and 69 (31.4%) had metachronous cancers after esophagectomy.

Survival and prognostic factors

One hundred and eight patients died of other diseases and the remaining 112 were alive at the end of the follow-up period. The median survival time of the 220 patients was 180 months and the overall 10-, 15-, and 20-year survival rates were 71.6, 50.1, and 32.2%, respectively. Univariate analysis revealed that 9 variables were as potential prognostic factors for patients cured of esophageal cancer (Table 2). No tumor characteristics were selected as prognostic factors in these patients. A total of 12 factors including three contentious variables were entered into the multivariate model, which revealed 8 independent prognostic factors (Table 3).

Cause of death

Of 108 patients who died of other diseases, 27 (25.0%) died of other cancers and 81 (75.0%) of diseases other than cancer. Specifically, head and neck cancer (8.3%) was the leading cause of other primary cancer deaths, followed by lung (5.6%) and gastric (2.8%) cancer. On the other hand, pulmonary diseases (30.6%) accounted for most other disease deaths, followed by senility (10.2%) and cardiovascular diseases (5.6%). Of the 20 patients who received radiotherapy, 5 died of cancer in the irradiated field, 3 of acute heart failure, and one of late radiation-induced toxicity. The leading causes of death in patients with above prognostic factors were shown in Table 4.

DISCUSSION

We conducted this study to identify the prognostic factors in patients cured of esophageal cancer after esophagectomy. To the best of our knowledge, this is the first study to elucidate that the independent prognostic factors for poor survival in this patient population are age at surgery, being male, pulmonary comorbidities, synchronous presence of other cancers, colonic/jejunal interposition, perioperative blood transfusion, pulmonary complications, and adjuvant radiotherapy.

Pulmonary complications, including postoperative pneumonia, were the most common complications in the short term. Thorough mediastinal lymph node dissection causes irreversible destruction of the neurovascular networks of the tracheobronchial tree, which can lead to deteriorated postoperative pulmonary function and increase the incidence of not only pulmonary complications but also community-acquired pneumonia over long-term follow-up. [18-20] This sequence of events supports our finding that the development of postoperative complications correlated significantly with the number of lymph nodes removed. Similarly, the fact that pulmonary diseases were the most common cause of death in patients cured of esophageal cancer may support this notion about the adverse consequences of mediastinal lymph node dissection, although it is central to improving the survival of these patients.

The presence of pulmonary comorbidities was also identified as an independent prognostic factor. Several reports have indicated that pulmonary comorbidities correlate strongly with severe complications after esophagectomy; [18, 20] however, only 4 of the 21 patients with pulmonary comorbidities in the present population developed postoperative pulmonary complications. Meticulous attention to postoperative management enabled patients with pulmonary comorbidities to survive the

postoperative period without pulmonary complications, even though the extent of lymphadenectomy was the same as in those without pulmonary comorbidities. Another possible explanation is that those patients with pulmonary comorbidities who had pulmonary complications died early in the postoperative period and were thus excluded from this study. In either case, pneumonia was the leading cause of death in patients with pulmonary comorbidities or pulmonary complications, and therefore careful follow up and patient education is required for patients who survive for more than 5 years.

The causes of death among patients who received radiotherapy, namely, cancer in the irradiated field, acute heart failure, and late radiation-induced toxicity, are of great concern. Radiotherapy for patients with esophageal cancer might increase the risk of developing secondary cancers in the larynx, lung, and thyroid [21]. Similarly, irradiation of the mediastinum or lung has been reported to cause cardiovascular events or radiation pneumonitis as late complications. [22, 23] In addition, radiotherapy may impair the host immune system. [24] All of these factors might have contributed to the present findings. Taken together, cured esophageal cancer patients who have previously received radiotherapy should be followed up carefully over the long term.

Irrespective of radiotherapy, patients with esophageal cancer have a strong tendency to develop other primary cancers, especially head and neck, lung, and gastric cancers. [9, 22, 25] In our study, the presence of synchronous cancer was one of the prognostic factors identified, but was not itself a cause of death. On the other hand, 61 patients (27.7%) developed other cancers during the follow-up period after esophagectomy, 27 of whom (43.3%) died as a result. Bamba et al.[7] reported that periodic endoscopy during long-term follow up after esophagectomy can improve prognosis by detecting gastric tube cancer during the potentially curative stage.

Systematic follow up focusing on the aerodigestive tract is required in patients cured of esophageal cancer, especially those with a history of other primary cancers. However, adequate intervals and follow-up periods are issues that need to be resolved.

Although age at surgery, being male, perioperative blood transfusion, and colonic/jejunal interposition were selected as independent prognostic factors in this study, it is uncertain whether these factors do in fact affect patient survival. Age and sex have been reported as strong prognostic factors within 5 years of esophagectomy. [26-28] However, the results of the present study might only reflect the age- and sex-related life expectancy of long-term survivors after esophagectomy, which is a similar finding to the observation that elderly men in an average population typically have shorter life expectancy than women of the same age. Blood transfusion may be related to impaired immunity, [29, 30] which may in turn lead to relapse of a micrometastatic disease, or the development of a secondary primary cancer or infectious disease such as pneumonia. However, it is unclear whether the effects of a blood transfusion will last for more than 5 years after surgery. Patients who underwent colonic/jejunal interposition were often predisposed to a deteriorated nutritional status and compromised immunity over the long term because of their history of gastrectomy, which might imply that this reconstruction is not a negative prognostic factor itself. Further investigation is required to elucidate the correlation between these factors and long-term survival after esophagectomy.

Limitations of this study are its retrospective, single-center design and substantial data missing during the long-term follow-up period, the effects of which might not have been negligible. For example, smoking may be the most common cause of lung diseases or secondary cancers and, therefore, should have been evaluated in this

study. However, data on smoking habits were not included because they were missing in many patients, especially after surgery. Furthermore, because this study aimed to assess the clinical course to identify factors affecting the survival of patients who were regarded as being cured of esophageal cancer, we selected patients with a relapse-free survival time of more than 5 years; selection bias was thus inevitable in this study design. Despite these limitations and considering the practically difficulties in conducting a prospective study, we believe that the present results are clinically significant to the management of long-term survivors of esophageal cancer after esophagectomy.

In conclusion, age at surgery, being male, synchronous cancers, colonic/jejunal interposition, perioperative blood transfusion, pulmonary comorbidities and complications, and radiotherapy were revealed as independent prognostic factors in patients cured of esophageal cancer after esophagectomy. Moreover, pulmonary diseases and other primary cancers were the most common causes of death. Careful follow up including the surveillance of other primary cancers is required even for long-term survivors, especially those with the abovementioned prognostic factors.

DISCLOSURE The authors declare no conflicts of interest.

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TABLE 1 Patients and tumor characteristics

Characteristics	Number of patients (%)
Age at esophagectomy*	63 years (44-84)
Gender	
Male	191 (86.8)
Female	29 (13.2)
Body weight at esophagectomy*	55.0 kg (37.0-86.0)
Body weight reduction rate for five years*	12.4% (-16.3-35.7)
Comorbidities	
Pulmonary	21 (9.5)
Cardiovascular	17 (7.7)
Renal	16 (7.3)
Diabetes mellitus	14 (6.4)
Cerebral and Psychiatric	13 (5.9)
Hepatic	13 (5.9)
Synchronous presence of other cancers	23 (10.5)
Tumor location (UICC)	
Upper thoracic	11 (5.0)
Mid-thoracic	125 (56.8)
Lower thoracic	84 (38.2)
Histology	
Squamous cell carcinoma	208 (94.5)

Non-squamous cell carcinoma	12 (5.5)
Histopathological grading (UICC)	
G1	67 (30.5)
G2	122 (55.5)
G3	23 (10.4)
G4	0
GX	8 (3.6)
Tumor depth (UICC)	
pT1	124 (56.4)
pT2	28 (12.7)
pT3	64 (29.1)
pT4	4 (1.8)
Lymph node metastasis (UICC)	
pN0	144 (65.5)
pN1-3	76 (34.5)

*Values depicted are median and range.

UICC, Union for International Cancer Control

TABLE 2 Univariate analysis using the log-rank test

Variable	n	MST (month)	*P* value
Gender			0.01
Male	191	161	
Female	29	233	
BW reduction rate for five years			0.47
≥ 10%	112	176	
< 10%	108	189	
Comorbidities			
Pulmonary			< 0.01
Presence	21	141	
Absence	199	189	
Cardiovascular			0.32
Presence	17	141	
Absence	203	183	
Renal			< 0.01
Presence	16	105	
Absence	204	188	
Diabetes mellitus			0.04
Presence	14	131	
Absence	206	185	
Liver			0.67

Presence	13	207	
Absence	207	180	
Cerebral			0.62
Presence	13	142	
Absence	207	185	
Synchronous cancers			< 0.01
Presence	23	118	
Absence	197	189	
Histological type			0.13
Squamous cell carcinoma	208	177	
Non-squamous cell carcinoma	12	260	
Tumor depth (UICC)			0.77
pT1-2	152	176	
pT3-4	68	185	
Lymph node metastasis (UICC)			0.67
pN0	144	180	
pN1-3	76	194	
Surgical procedure			0.56
Transthoracic esophagectomy	140	183	
Transhiatal esophagectomy	80	180	
Lymphadenectomy			0.70
Three field	91	188	
Others	129	161	

Reconstruction route			0.79
Posterior mediastinal	66	191	
Retrosternal, Subcutaneous	154	183	
Reconstruction organ			< 0.01
Gastric tube	194	189	
Colon/Jejunum	26	131	
Perioperative blood transfusion			< 0.01
Done	161	154	
Not done	59	293	
Postoperative complications			
Recurrent laryngeal nerve palsy			0.57
Presence	102	194	
Absence	118	162	
Pulmonary complications			< 0.01
Presence	48	141	
Absence	172	189	
Anastomotic leakage			0.81
Presence	41	142	
Absence	179	185	
Chemotherapy alone			0.24
Performed	69	202	
Not performed	151	161	
Radiotherapy ± chemotherapy*			0.04

Performed	20	131
Not performed	200	189

UICC, Union for International Cancer Control

*Radiotherapy alone or concurrent with chemotherapy was performed in 5 or 15 patients, respectively.

TABLE 3 Multivariate analysis by the Cox proportional hazard model

Variable	Hazard ratio	95% confidence interval	*P* value
Age at surgery	1.05	1.02-1.09	< 0.01
Male	2.62	1.18-5.83	0.02
Body weight	0.97	0.94-1.00	0.05
Pulmonary comorbidities	2.03	1.11-3.74	0.02
Renal comorbidities	1.99	0.94-4.21	0.07
Diabetes mellitus	1.83	0.86-3.92	0.12
Synchronous cancers	2.35	1.30-4.25	< 0.01
Number of lymph nodes removed	1.00	0.99-1.00	0.27
Colonic/jejunal interposition	1.76	1.05-2.95	0.03
Blood transfusion	1.92	1.10-3.34	0.02
Pulmonary complications	1.71	1.08-2.72	0.02
Radiotherapy	2.13	1.19-3.80	0.01

TABLE 4 Leading causes of death in each variable

Variable	n	Leading causes of death	
Male	191	Pneumonia	30 (15.7%)
		Other cancers	26 (13.6%)
Pulmonary comorbidities	21	Pneumonia	8 (38.1%)
		Other cancers	3 (14.3%)
Synchronous cancers	23	Pneumonia	5 (21.7%)
		Other cancers	4 (17.4%)
Colonic/jejunal interposition	26	Pneumonia	5 (19.2%)
		Other cancers	5 (19.2%)
Blood transfusion	161	Other cancers	24 (14.9%)
		Pneumonia	22 (13.7%)
Pulmonary complications	48	Pneumonia	10 (20.8%)
		Other cancers	6 (12.5%)
Radiotherapy	20	Other cancers	5 (25.0%)
		Heart failure	3 (15.0%)