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# Evolution of Treatment Outcomes and Prognostic Factors in Esophageal Cancer Surgery

## *A Retrospective Analysis of 1500 Consecutive Esophagostomies*

Yasue Kimura, MD, PhD, Eiji Oki, MD, PhD, Tomonori Nakanoko, MD, PhD, Qingjiang Hu, MD, PhD, Keita Natsugoe, MD, Sho Nanbara, MD, PhD, Ryota Nakanishi, MD, PhD, Yuichiro Nakashima, MD, PhD, Mitsuhiko Ota, MD, PhD, and Tomoharu Yoshizumi, MD, PhD

**Objective:** To clarify the surgical outcomes of esophagectomy in Japan and comprehensively evaluate trends over time. It is important to analyze data from a large number of consecutive patients from a single institution.

**Methods:** We evaluated the treatment outcomes, complications, and prognosis of 1500 consecutive patients who underwent esophagectomy during 5 periods: group A (n = 284), 1964–1984; group B (n = 345), 1985–1993; group C (n = 253), 1994–2002; group D (n = 297), 2003–2012; and group E (n = 321), 2013–March 2020.

**Results:** The incidences of squamous cell carcinoma and adenocarcinoma were 93.8% and 3.3%, respectively. The proportion of adenocarcinoma cases has gradually increased over time. The in-hospital mortality rates for groups A, B, C, D, and E were 12%, 4.6%, 1.2%, 2.9%, and 1.5%, respectively. Group A had a significantly higher mortality rate than the other groups ($P < 0.0001$). Three-year survival rates were 22.2%, 47.8%, 53.4%, 69.9%, and 72.6% in groups A–E, respectively, 5-year survival rates were 17.2%, 41.3%, 49.2%, 63.9%, and 68.4%, respectively ($P < 0.0001$, group A *vs* groups D and E). The prognosis improved over time. Multivariate analysis revealed that depth of invasion, lymph node metastasis, the extent of lymph node resection, curative resection, pulmonary complications, and anastomotic leakage were significant independent prognostic factors. However, for recent surgeries (groups D and E), only the depth of invasion, lymph node metastasis, and curative resection were significant independent prognostic factors.

**Conclusions:** Valuable changes in background and prognostic factors occurred over time. These findings will help optimize esophageal cancer management and improve patient outcomes.

**Keywords:** esophageal cancer, esophagectomy, prognostic factors

Esophageal cancer is the ninth most common cancer and the sixth leading cause of cancer-related death worldwide.[1] Esophageal cancer is a highly aggressive cancer with a poorer prognosis than other gastrointestinal cancers.[2–4] Esophagectomy for esophageal cancer is the treatment with the best chance of cure and remains the standard treatment. When esophagectomy was first introduced, it was highly invasive surgery and was associated with high mortality and morbidity. However, dramatic advances in diagnostic techniques, perioperative systemic management, implementation of radical esophagectomy with curative intent, extensive lymph node resection, widespread use of minimally invasive surgery, and multidisciplinary treatment combining chemotherapy and radiation therapy have greatly improved the treatment outcomes.[5–13] As a result, the 5-year survival rate is approximately 60%, and mortality and morbidity rates have also improved markedly.[14]

In Western countries, esophageal adenocarcinoma is the predominant type of esophageal carcinoma, occurring mostly in the lower esophagus and gastroesophageal junction.[3,15] In contrast, in Japan, the incidence of squamous cell carcinoma is >90% and 50% of esophageal cancers are located in the middle thoracic esophagus. Recently, the incidence of adenocarcinoma of the lower esophagus and gastroesophageal junction has increased in Japan, and there has been a corresponding change in the characteristics of affected patients.[14,16]

Morita et al reported the surgical outcomes of 1000 cases of esophageal cancer in 2008.[17] More than 10 years since that report, minimally invasive surgery, such as thoracoscopic and robotic surgery, has become widely used, and esophageal cancer treatment has changed rapidly. Additionally, since 2020, immune checkpoint inhibitors (ICIs) have become available for esophageal cancer therapy in Japan. Therefore, the treatment of esophageal cancer has undergone major changes, and treatment outcomes are expected to change in the future.

To evaluate the progress of esophageal cancer treatment, it is important to analyze the clinical outcomes of consecutive cases at a single institution using a reliable database. In our department, a database of patients treated for esophageal cancer was

*From the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.*

*The authors declare that they have nothing to disclose.*

*Data usage requires a formal process.*

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*Reprints: Yasue Kimura, MD, PhD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Email: kimura.yasue.740@m.kyushu-u.ac.jp.*



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established in 1964, with detailed clinicopathological and follow-up data. Therefore, this study aimed to analyze changes in patient background factors, treatment outcomes, mortality, morbidity, and prognosis using data from 1500 consecutive Japanese patients with esophageal cancer who underwent esophagectomy at our institution.

## PATIENTS AND METHODS

### *Patients*

This study evaluated data from 1500 patients who underwent esophagectomy for esophageal cancer between December 1964 and March 2020 at our institute. The patients comprised 1280 men and 220 women, with a mean age of 62.9 years (range: 35–90 years). Histological diagnosis showed that the main lesions were squamous cell carcinoma in 1407 patients, adenocarcinoma in 50 patients, and other histological types (undifferentiated, neuroendocrine tumor, and others) in 43 patients. Survival data were updated in March 2023. Follow-up evaluations were performed 3 to 32 years after the primary surgery (median observation period, 4.2 years for censored patients), with data available for all patients. From 1964 to 1980, there were less than 20 esophagostomies per year; however, after 1981, there were more than 20 esophagostomies per year, and after 2015, there were approximately 50. Group A comprised 284 patients who underwent esophagectomy between 1964 and 1984, group B comprised 345 patients who underwent esophagectomy between 1985 and 1993, group C comprised 253 patients who underwent esophagectomy between 1994 and 2002, group D comprised 297 patients who underwent esophagectomy between 2003 and 2012, and group E comprised 321 patients who underwent esophagectomy between 2013 and March 2020. The classification of the range of years for each group was based on the chief surgeons or introduction of a new surgical procedure in esophageal cancer.

This study was approved by the Human Research Review Committee of Kyushu University (Approval No 2019-212).

### *Tumor Staging*

The database was updated in accordance with the 12th edition of the Japanese classification of esophageal cancer according to clinicopathological factors and the eighth edition of the tumor-node-metastasis (TNM) classification defined by the Union for International Cancer Control for tumor staging.[18] The depth of invasion and lymph node metastasis were defined by histological examination of surgically resected specimens. Postoperative histological T- and N-factors could not be evaluated in some special histological types of lesions. In patients who received preoperative radiotherapy, the microscopic distribution of viable cancer cells, scar tissue, and disappearance of normal structures, such as the lamina propria and muscularis propria, were used to define the depth of invasion.

### *Surgical Procedures*

Resection and reconstruction of esophageal cancer was performed by subtotal esophagectomy with cervical anastomosis (McKeown), esophagectomy with thoracic anastomosis (Ivor–Lewis method), blunt esophagectomy, and other methods. Approaches included right open thoracotomy, thoracoscopy, mediastinoscopy, and robotic surgery. For tumors located mainly in the abdominal esophagus and invading the lower thoracic esophagus (esophageal invasion length less than 2 cm), lower esophagectomy, and reconstruction with a gastric tube or a pediculate jejunum were performed using the left thoracoabdominal or abdominal approach only. Blunt or mediastinoscopic resection via cervical and abdominal approaches is occasionally performed as an alternative in cases where impaired lung function from chronic obstructive pulmonary disease or postoperative lung cancer makes open surgery challenging. Cervical esophagectomy and laryngectomy are performed for cervical esophageal cancer, and total pharyngolaryngoesophagectomy is sometimes performed for patients with thoracic esophageal cancer.

For thoracic esophageal cancer, 3-field lymphadenectomy is usually performed, with dissection to include the cervical, mediastinal, and abdominal lymph nodes. In the early 1980s, radical dissection of lymph nodes in the upper mediastinum, including those along the right and left recurrent laryngeal nerves, became a routine procedure. Since 1988, 3-field lymphadenectomy has been performed for TNM stages I–III upper and middle thoracic esophageal cancer in patients younger than 75 years and at low operative risk.

The stomach was used as the basic reconstructive organ unless the patient had undergone a previous gastrectomy or had gastric cancer. In this case, the right hemicolon was used. The subcutaneous route was routinely used when esophagectomies were first performed in our department. Subsequently, the posterior mediastinal route (intrathoracic) was the first choice. However, we experienced severe pulmonary complications due to anastomotic leakage or gastrotracheal fistula along the posterior mediastinal route. Therefore, the retrosternal route is the basic reconstruction route.

### *Postoperative Management*

Mechanical ventilation was performed and the patient was managed in the intensive care unit. To prevent pneumonia, sputum suctioning by bronchoscopy is performed frequently, and aggressive pulmonary rehabilitation is performed. However, after the introduction of thoracoscopic surgery in 2010, the patient awakened in the operating room on the same day, extubated, and transferred to the intensive care unit. Pulmonary complications, anastomotic leakage, and other complications were evaluated in accordance with the Clavien–Dindo classification published in 2004,[19] with Grade III and above classified as complications.

### *Statistical Analysis*

Differences in distribution frequency between groups were evaluated using Fisher's exact test or unpaired *t*-test. Survival curves were plotted using the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test and Cox proportional hazards model. Multivariate analysis using a Cox proportional hazards model was used to identify independent prognostic factors.

## RESULTS

### *Clinical Features*

Table 1 summarizes the patients' clinical background for each group. Group E was significantly older than groups A, B, and C ($P < 0.0001$), and group D ($P = 0.0003$). The main tumor was located significantly more frequently in the cervical esophagus in group E than in the other groups ($P < 0.0001$). Histologically, squamous cell carcinoma accounted for approximately 94% of all cases, while the rate of adenocarcinoma diagnosis increased to 6% in group E ($P = 0.047$).

The proportion of adenocarcinomas has been increasing in national surveys,[14] as in our cohort, indicating changes in the esophageal cancer population in Japan since the 2010s. When comparing our groups, groups A and B had a higher proportion of advanced cancers, whereas groups D and E had a higher proportion of early-stage cancers, with stage I accounting for

**TABLE 1.**

**Clinicopathological Characteristics of the 1500 Patients Who Underwent Esophagectomy**

| Factor | No. of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| | Group A (n = 284) | Group B (n = 345) | Group C (n = 253) | Group D (n = 298) | Group E (n = 320) | Total (n = 1500) |
| Age (mean ± SD)* | 62.4 ± 8.4 | 63.1 ± 9.9 | 62.9 ± 8.7 | 63.8 ± 9.2 | 66.4 ± 8.7 | 63.8 ± 7.9 |
| Sex | | | | | | |
| Male | 231 (81.3) | 303 (87.8) | 226 (89.3) | 252 (87.6) | 268 (83.8) | 1280 (85.9) |
| Female | 53 (18.7) | 42 (12.2) | 60 (10.7) | 46 (12.4) | 52 (16.2) | 220 (14.1) |
| Tumor location† | | | | | | |
| Ce | 14 (4.9) | 15 (4.3) | 13 (5.2) | 30 (10.1) | 41 (12.8) | 113 (7.5) |
| Ut | 25 (8.8) | 39 (11.3) | 26 (10.3) | 46 (15.5) | 50 (15.6) | 186 (12.4) |
| Mt | 170 (59.9) | 221 (61.2) | 130 (51.4) | 119 (40.1) | 137 (42.7) | 767 (51.1) |
| Lt | 50 (17.6) | 59 (17.1) | 63 (24.9) | 92 (40.1) | 75 (23.4) | 339 (22.6) |
| Ae | 25 (8.8) | 21 (6.1) | 21 (8.3) | 10 (3.4) | 18 (5.6) | 95 (6.3) |
| Histology‡ | | | | | | |
| SCC | 272 (95.8) | 330 (95.7) | 234 (95.8) | 282 (91.3) | 289 (90.3) | 1407 (93.8) |
| Adenocarcinoma | 5 (1.7) | 8 (2.3) | 8 (3.2) | 14 (3.0) | 20 (6.3) | 50 (3.3) |
| Other | 7 (2.4) | 7 (2.0) | 11 (4.3) | 7 (2.3) | 11 (3.4) | 43 (2.9) |
| pT†§ | | | | | | |
| pTis,0,1,2 | 64 (22.5) | 139 (40.3) | 121 (47.8) | 137 (45.8) | 187 (57.2) | 644 (42.9) |
| pT3,4 | 220 (77.5) | 206 (59.7) | 132 (52.2) | 161 (54.2) | 137 (42.8) | 856 (57.1) |
| Lymph node metastasis†§ | | | | | | |
| Positive | 115 (40.5) | 200 (58.0) | 140 (55.3) | 166 (53.9) | 183 (57.0) | 798 (53.2) |
| Negative | 169 (59.5) | 145 (42.0) | 113 (44.7) | 137 (46.1) | 138 (43.0) | 702 (46.8) |
| pTNM stage†§ | | | | | | |
| Stage 0 | 0 | 5 (1.5) | 4 (1.6) | 2 (0.7) | 5 (1.6) | 16 (1.1) |
| Stage IA | 1 (0.3) | 23 (6.7) | 22 (8.7) | 21 (7.0) | 39 (12.2) | 106 (7.0) |
| Stage IB | 14 (4.9) | 46 (13.3) | 36 (14.2) | 48 (16.4) | 59 (18.5) | 203 (13.4) |
| Stage IIA | 20 (18.3) | 30 (20.3) | 22 (25.3) | 26 (25.8) | 16 (5.0) | 110 (7.3) |
| Stage IIB | 52 (28.4) | 70 (28.4) | 64 (28.4) | 77 (28.4) | 73 (22.8) | 335 (22.3) |
| Stage IIIA | 20 (7.0) | 21 (6.1) | 18 (7.1) | 19 (6.4) | 25 (7.8) | 103 (6.9) |
| Stage IIIB | 152 (53.5) | 138 (40.0) | 78 (30.8) | 100 (33.6) | 69 (21.5) | 537 (35.8) |
| Stage IVA | 5 (1.8) | 2 (0.6) | 5 (1.9) | 2 (0.7) | 31 (9.7) | 45 (3.0) |
| Stage IVB | 19 (6.7) | 10 (2.8) | 4 (1.6) | 2 (0.67) | 1 (0.3) | 36 (2.4) |
| Curability† | | | | | | |
| Curative | 144 (50.7) | 232 (67.2) | 198 (78.3) | 264 (88.9) | 293 (91.3) | 1131 (75.4) |
| Noncurative | 140 (49.3) | 113 (32.8) | 55 (21.7) | 33 (11.1) | 28 (8.7) | 369 (24.6) |

*$P < 0.0001$ for group E compared with groups A, B, and C, respectively; $P = 0.0003$ for group D.

†$P < 0.0001$.

‡$P = 0.0047$.

§UICC eighth edition.

Ae indicates abdominal esophagus; Ce, cervical; Lt, lower thoracic; Mt, middle thoracic; pTis, pathological tumor in situ; pTNM, pathological tumor, node, metastasis; SCC, Squamous cell carcinoma; SD, standard deviation; UICC, Union for International Cancer Control; Ut, upper thoracic.

approximately 30%. Over time, the percentage of early-stage cancers has increased. The accuracy of preoperative imaging procedures such as endoscopy and computed tomography is likely strongly reflected in these findings. Because of this improved accuracy, the proportion of radical resection cases increased gradually.

Table 2 lists the treatment details. Preoperative treatment was initiated in group A, and there were no differences between the groups. Regarding the resection and reconstruction methods, the majority of patients in groups A–C underwent thoracic anastomosis, whereas those in groups D and E underwent McKeown's method. This is related to the fact that lymphadenectomy of the superior mediastinum and cervical dissection became standard over the study period. The methods of thoracotomy also changed over time, with the numbers of thoracoscopic and robotic procedures gradually increasing over time and were highest in groups D and E. In fact, open thoracotomy has not been performed in our department since 2020. There was only 1 case of robotic surgery in group C, which was one of a series of various robotic procedures performed at our department in 2001.[20]

Although the basis of lymphadenectomy is 3-field lymphadenectomy, this was not performed in at-risk patients aged >75 years, and the number of patients who underwent this procedure decreased to approximately 30% in the years in group E owing to the high number of elderly patients.

The stomach was used as the major reconstructive organ during all periods. The reconstruction route was changed in accordance with the policy during each period, with the subcutaneous route being used routinely in the past. This was because anastomotic leakage was common and needed to be managed. Next period, the posterior mediastinal route was chosen as the physiologic route. However, we experienced severe pulmonary complications due to anastomotic leakage or gastrotracheal fistula along the posterior mediastinal route. As a result, in recent periods, the retrosternal route has been the primary route.

### Postoperative Complications

Table 3 shows the postoperative complications and in-hospital mortality rates. Postoperative complications occurred in 583 (38.9%) patients. The incidence of postoperative complications

**TABLE 2.**
**Treatments Performed for Esophageal Cancer**

| | No. of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Group A (n = 284)** | **Group B (n = 345)** | **Group C (n = 253)** | **Group D (n = 298)** | **Group E (n = 320)** | **Total (n = 1500)** |
| Preoperative treatment* | | | | | | |
| Yes | 208 (73.3) | 226 (65.5) | 143 (56.5) | 134 (45.1) | 196 (61.1) | 907 (60.5) |
| Method of esophagostomy | | | | | | |
| McKeown | 224 (78.9) | 226 (65.5) | 96 (37.9) | 254 (85.2) | 307 (96.3) | 1107 (73.8) |
| Ivor–Lewis | 46 (17.6) | 100 (30.1) | 142 (58.1) | 12 (6.7) | 0 (1.5) | 300 (20.0) |
| Cervical esophagectomy | 10 (3.5) | 2 (0.6) | 7 (2.6) | 20 (6.7) | 8 (2.5) | 47 (3.1) |
| Transhiatal esophagectomy | 4 (3.5) | 4 (0.6) | 5 (2.6) | 8 (6.7) | 5 (2.5) | 26 (1.7) |
| Blunt | 0 | 13 (3.8) | 3 (1.2) | 4 (1.3) | 0 | 20 (1.3) |
| Approach† | | | | | | |
| Open thoracotomy | 270 (95.1) | 326 (94.5) | 237 (93.7) | 252 (84.8) | 45 (14.1) | 1130 (75.4) |
| Thoracoscopic | 0 (0) | 0 (0) | 0 (0) | 14 (4.7) | 219 (68.2) | 233 (15.6) |
| Robot-assisted | 0 (0) | 0 (0) | 1 (0.4) | 0 (0) | 39 (12.2) | 40 (1.4) |
| Transhiatal | 4 (1.4) | 4 (1.2) | 5 (2.0) | 8 (2.7) | 5 (1.5) | 26 (1.3) |
| Cervical | 10 (3.5) | 2 (0.6) | 7 (2.8) | 19 (6.7) | 9 (2.5) | 47 (3.1) |
| Mediastinal | 0 (0) | 13 (3.8) | 3 (2.7) | 4 (1.3) | 4 (2.8) | 24 (0.3) |
| Lymphadenectomy‡ | | | | | | **(n = 1431)** |
| Two-field | 272 (100) | 282 (85.5) | 282 (77.8) | 282 (52.9) | 239 (66.8) | 1097 (76.7) |
| Three-field | 0 | 48 (15.5) | 54 (22.2) | 129 (47.1) | 103 (33.2) | 334 (23.3) |
| Organ used for reconstruction§ | | | | | | |
| Stomach | 231 (81.3) | 315 (91.3) | 218 (86.2) | 240 (80.8) | 286 (87.0) | 1274 (84.9) |
| Colon | 18 (6.3) | 18 (5.2) | 17 (6.7) | 29 (9.7) | 15 (4.7) | 97 (6.5) |
| Jejunum | 23 (9.1) | 8 (2.5) | 16 (5.6) | 27 (5.6) | 18 (5.1) | 92 (6.1) |
| Other | 5 (5.6) | 0 | 0 | 0 | 0 | 391 (90.5) |
| Route of reconstruction‖ | | | | | | |
| Subcutaneous | 214 (75.4) | 129 (37.4) | 86 (34.0) | 75 (25.3) | 9 (2.8) | 513 (34.2) |
| Retrosternal | 14 (4.9) | 93 (27.0) | 1 (0.4) | 111 (56.1) | 229 (71.3) | 448 (29.9) |
| Intrathoracic | 30 (10.6) | 110 (29.0) | 142 (56.1) | 12 (4.0) | 0 | 284 (18.9) |
| Posterior mediastinum | 0 | 14 (4.1)† | 10 (4.0) | 71 (24.0) | 67 (20.9) | 162 (10.8) |
| Others | 14 (4.9) | 5 (1.4) | 12 (4.6) | 27 (9.0) | 14 (4.3) | 72 (4.7) |

*Treatment comprising neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, definitive chemoradiotherapy.
†Mediastinal approach including blunt and mediastinoscopic approaches.
‡Excludes the following cases: cervical esophagectomy, transhiatal esophagectomy, blunt, and patients with other histological diagnoses.
§Excludes unreconstructed 16 cases.
‖$P < 0.001$ compared with group A by Fisher's exact test.

**TABLE 3.**
**Morbidity and Mortality**

| | No. of Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| **Morbidity and In-Hospital Mortality** | **Group A (n = 284)** | **Group B (n = 345)** | **Group C (n = 253)** | **Group D (n = 298)** | **Group E (n = 320)** | **Total (n = 1500)** |
| Postoperative complications: Yes | | | | | | |
| All complications* | 164 (57.7) | 121 (35.1) | 80 (32.3) | 96 (32.3) | 12 (38.0) | 583 (38.9) |
| Pulmonary complications† | 104 (36.6) | 34 (9.8) | 34 (13.4) | 31 (10.4) | 32 (9.9) | 235 (15.7) |
| Anastomotic leakage‡ | 93 (32.7) | 96 (27.8) | 45 (17.8) | 57 (19.2) | 38 (11.9) | 329 (21.9) |
| In-hospital mortality§ | | | | | | |
| Total | 28 (12.0) | 22 (4.6) | 3 (1.2) | 9 (2.9) | 5 (1.5) | 67 (4.5) |
| Within 30 days | 19 (6.7) | 6 (1.7) | 0 (0) | 1 (0.3) | 1 (0.3) | 40 (2.7) |
| After 30 days | 15 (5.3) | 10 (2.9) | 3 (1.2) | 8 (2.6) | 4 (1.2) | 27 (1.8) |

*Group A; significantly higher incidence compared with the other groups ($P < 0.0001$, Fisher's exact test).
†Group A; significantly higher incidence compared with the other groups ($P < 0.0001$; Fisher's exact test).
‡Group E; significantly lower incidence compared with groups A, B, and C ($P < 0.0001$) and group D ($P = 0.039$) (Fisher's exact test).
§Group A; significantly higher incidence compared with the other groups ($P < 0.0001$; Fisher's exact test).

was 57.7% in group A and remained at approximately 35% in groups B–E ($P < 0.0001$). Pulmonary complications occurred in 36.6% of group A patients but decreased significantly to approximately 10% in groups B–E ($P < 0.0001$). The incidence of anastomotic leakage decreased gradually and was significantly lower in group E than in groups A, B, C ($P < 0.0001$), and D ($P = 0.039$). The in-hospital mortality rate decreased gradually, with group A at 12% and 4.6%, 1.2%, 2.9%, and

1.5% in groups B, C, D, and E, respectively, and significant differences were present between group A and the other groups ($P<0.0001$).

The 30-day mortality rate decreased over time, and in groups A and B, most deaths were due to complications. However, from group D onward, deaths were unrelated to surgical complications but instead to acute vascular events, such as brain diseases.

### Survival Analysis

Overall survival (OS) and Kaplan–Meier survival curves are shown in Figure 1. Three-year OS rates in groups A–E were 22.2%, 47.8%, 53.4%, 69.9%, and 72.6%, respectively, and the 5-year OS rates were 17%, 41.3%, 49.2%, 63.9%, and 68.4%, respectively. Prognosis improved significantly with age, with no significant difference between groups D and E (log-rank: group E *vs* groups A, B, and C; $P<0.0001$). The hazard ratios and 95% confidence intervals (95% CI) for group E compared with groups A, B, C, and D are as follows: 4.70 (3.64–6.02), $P<0.0001$; 2.21 (1.719–2.832), $P<0.0001$; 1.80 (1.375–2.36), $P<0.0001$; and 1.10 (0.825–1.465), $P=0.5167$, respectively.

To identify independent prognostic factors after esophagectomy, univariate and multivariate analyses were performed using the Cox proportional hazards model (Table 4). The independent prognostic factors indicating good prognosis were shallow depth of invasion, absence of lymph node metastasis, 3-field lymphadenectomy, curative resection, absence of pulmonary complications, and anastomotic leakage. Figure 2 shows the OS after esophagectomy with depth of invasion (Fig. 2A), lymph node metastasis (Fig. 2B), 2- or 3-field lymphadenectomy (Fig. 2C), and curative resection (Fig. 2D).

Because there was no difference in prognosis between groups D and E, we limited our analysis of prognostic factors to the time periods of groups D and E. Figure 3 shows the OS after esophagectomy with depth of invasion (Fig. 3A), lymph node metastasis (Fig. 3B), 2- or 3-field lymphadenectomy (Fig. 3C), and radical resection (Fig. 3D) in groups D and E. The results of the analysis of the independent prognostic factors in groups D and E are shown in Table 5. Tumor location, depth of invasion, lymph node metastasis, and curative resection were significant prognostic factors in univariate analysis; however, only depth of invasion, lymph node metastasis, and curative resection were significant prognostic factors in multivariate analysis. Complications and 3-field lymphadenectomy were not prognostic factors in groups D and E after 2003.

## DISCUSSION

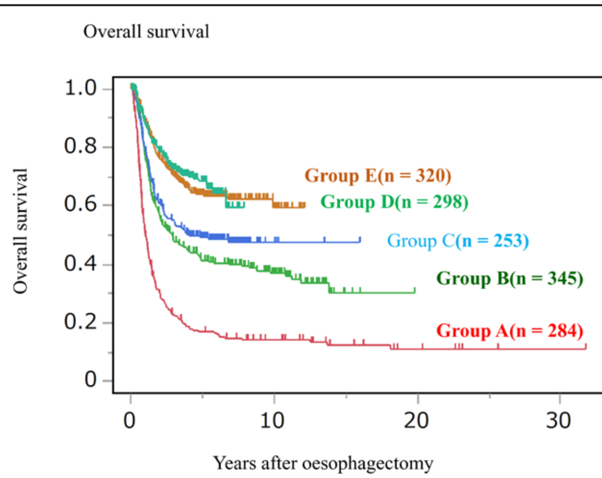
### Historical Evolution of Esophageal Cancer Surgical Treatment

The Japanese Esophageal Society (JES) has reported the treatment outcomes for esophageal cancer cases throughout Japan.[14] Additionally, the National Clinical Database registry was started in Japan in 2010, and the treatment outcomes of esophageal cancer surgery were analyzed and reported.[21] However, to evaluate the historical progress of surgical treatment for esophageal cancer, it is important to review the clinical results of a large number of consecutive patients treated at a single institution. Siewert and colleagues reported improved prognosis and decreased mortality.[22] Hofstetter et al revealed that preoperative chemoradiation may have contributed to improved survival.[23]

Our study analyzed a uniformly organized database of 1500 patients who underwent esophagectomy at our institution during the same period when esophageal cancer surgery was first performed in Japan. The analysis of data from this long period clearly demonstrates the current progress in the clinical outcomes of esophagectomy in Japan.

First, regarding changes in patients' backgrounds, squamous cell carcinoma of the upper or middle esophagus is dominant in Asian countries, including Japan, whereas adenocarcinoma of the lower esophagus and esophagogastric junction is more common in Western countries.[24] However, recently, there has also been a trend toward higher rates of adenocarcinoma of the esophagogastric junction in Japan as well.[14,16] The proportion of adenocarcinoma cases clearly increased over time (1.7% to 6.3% in group E), indicating changes in the esophageal cancer population in Japan since the 2010s. Esophageal adenocarcinoma is more common in the West, and its risk factors include diet, gastroesophageal reflux disease, and high body mass index.[24] Recently, social background and genetic factors have also been elucidated.[15] It is imperative to investigate the risk factors and potential etiologies of esophageal adenocarcinoma and squamous cell carcinoma in the Japanese population while also devising effective treatment strategies. Other changes in the patients' backgrounds included an increase in the proportion of elderly patients and an increase in early cancer rates. The increase in esophageal cancer among the elderly is considered to be a result of the aging population in Japan.[25]

The proportion of cervical and upper thoracic esophageal cancers also increased significantly over time. In the univariate analysis of groups D and E, the upper thoracic location was a significant poor prognostic factor. Although there is a possibility




| | | Hazard ratio (95%CI) | P-value |
|---|---|---|---|
| Group E | Group A | 4.70（3.64-6.02） | <.0001 |
| | Group B | 2.21(1.719-2.832) | <.0001 |
| | Group C | 1.80(1.375-2.363) | <.0001 |
| | Group D | 1.10(0.825-1.465) | 0.5167 |

**FIGURE 1.** Overall survival of the 1500 consecutive patients with esophageal cancer in this study. Group A had a significantly higher mortality rate compared with the other groups ($P<0.0001$). However, the hazard ratios (95% confidence intervals) for group E compared with groups A, B, C, and D are as follows: 4.70 (3.64–6.02), $P<0.0001$); 2.21 (1.719–2.832), $P<0.0001$; 1.80 (1.375–2.36), $P<0.0001$; and 1.10 (0.825–1.465), $P=0.5167$, respectively. CI indicates confidence interval.

**TABLE 4.**

**Analysis of the Prognostic Factors Using Cox Proportional Hazard Analysis**

| Factor | Object | Control | Univariate-Analysis | | Multivariate-analysis | |
|---|---|---|---|---|---|---|
| | | | Hazard Ratio (95% CI) | *P* | Hazard Ratio (95% CI) | *P* |
| Age (years) | <75 | ≥75 | 0.994 (0.792–1.278) | 0.962 | | |
| Sex | Male | Female | 1.168 (0.945–1.445) | 0.152 | | |
| Location of the tumor | Ce/Ut | Mt/Lt | 1.020 (0.849–1.228) | 0.825 | | |
| Depth of invasion | T0/1/2 | T3/T4 | 0.305 (0.258–0.361) | <0.0001 | 0.460 (0.340–0.565) | <0.0001 |
| Lymph node metastasis | Negative | Positive | 0.347 (0.294–0.399) | <0.0001 | 0.491 (0.315–0.516) | <0.0001 |
| Extent of lymphadenectomy | 2-field | 3-field | 1.618 (1.243–1.818) | <0.0001 | 1.513 (1.337–2.358) | <0.0001 |
| Resectability | R0 | R1 or R2 | 0.247 (0.212–0.288) | <0.0001 | 0.417 (0.283–0.525) | <0.0001 |
| Pulmonary complications | None | present | 0.612 (0.501–0.746) | <0.0001 | 0.763 (0.691–0.939) | 0.009 |
| Anastomotic leakage | None | present | 0.607 (0.514–0.717) | <0.0001 | 0.503 (0.548–0.975) | 0.027 |

Ce indicates cervical; CI, confidence interval; Lt, lower thoracic; Mt, middle thoracic; T, tumor; Ut, upper thoracic.

of changes in incidence, the proportion of cervical and upper thoracic esophageal cancer was only 14.6% in a JES report,[14] which is overwhelmingly different from our facility's rate of 28.4%. Therefore, we believe that the change in tumor location proportions is due to the fact that highly invasive surgeries, such as total pharyngo-laryngo-esophagectomy, can now be performed safely[26] for patients with cervical and upper thoracic esophageal cancer at institutes authorized by the JES.

### *Improvement in Surgical Outcomes and Contributing Factors*

The results of our study clearly demonstrate a significant improvement in the prognosis of patients who underwent esophagectomy. Many factors may have contributed to this remarkable improvement. First, advancements in diagnostic techniques, such as endoscopic examinations (iodine staining, endoscopic ultrasonography, narrow-band imaging), have led to an increase in the detection of early-stage cancer.[5,6] Detection of early-stage cancer is considered one of the factors contributing to the increase in curative resection. However, since the onset of the coronavirus disease outbreak in 2020, there has been a temporary increase in the proportion of advanced cancers in patients with esophageal cancer. The implications of this trend regarding treatment outcomes in the next 2000 cases remain unclear.

Second, there was a decrease in the overall complications, including pulmonary complications, over time. In our analysis of all the cases, pulmonary complications and anastomotic leakage were identified as prognostic factors. Since the 1980s, the incidence of postoperative complications, including in-hospital mortality, has decreased significantly. Previously, many surgical deaths were caused by severe pulmonary complications such as pneumonia and acute respiratory distress syndrome. Over time, it has become possible to reduce pulmonary complications by performing frequent postoperative suctioning of retained secretions in patients who cannot cough properly and by administering perioperative respiratory physiotherapy.[27–29] One of the reasons for the decrease in complications is the change in surgical methods. In the late 1980s, Ivor–Lewis esophagectomy was first performed in our department. The number of complications decreased during this period. Additionally, in the early 1990s, to promote early recovery of cough reflex, we decided to preserve the recurrent laryngeal nerve as much as possible during mediastinal lymphadenectomy. Minimally invasive surgery for esophageal cancer was first reported in 1992 and has spread rapidly worldwide.[7] Our department began performing complete thoracoscopic surgery in 2010. This minimally invasive surgery dramatically changed the postoperative management. Furthermore, robotic-assisted thoracoscopic esophagectomy is now more common, and its usefulness has been reported in many cases.[30] Advances in surgical techniques have greatly reduced the risk of pulmonary complications in patients with esophageal cancer.[31] In fact, we have performed minimally invasive surgery for esophageal cancer and robotic-assisted thoracoscopic esophagectomy exclusively since 2020. The widespread adoption of these procedures can be attributed to both the low rate of pulmonary complications and their significant surgical advantages.[32]

Anastomotic leakage is a prognostic factor in esophageal surgery, and various efforts have been made to reduce this complication.[26,33,34] In group D, there was a temporary increase in anastomotic leakage; however, in group E, the rate was <10%. The higher incidence of anastomotic leakage in group D can be attributed to the increased prevalence of cervical esophageal cancer and the greater utilization of colon reconstruction. We implemented several improvements,[26,35] resulting in a decrease in anastomotic leakage rates in group E. The rate of recent anastomotic leakage was <5%. Furthermore, the reduction in stenosis rates also contributes to patients' quality of life.[34]

### *Lymphadenectomy*

In the analysis of all cases, radical resection, including lymphadenectomy, was an important surgical prognostic factor. Esophageal cancer is often associated with lymph node metastasis to the mediastinal lymph nodes, as well as to the abdominal and cervical lymph nodes. Therefore, curative treatment involving mediastinal lymphadenectomy and cervical and abdominal lymphadenectomy is important. Since the early 1980s, patients with upper and middle thoracic esophageal cancer have undergone subtotal esophagectomy with radical dissection of the mediastinal and abdominal lymph nodes, and 3-field dissection with cervical dissection.[36,37] Morita et al reported that the prognosis of patients who underwent 3-field dissection was better than that of patients who underwent 2-field dissection, and a multivariate analysis showed that 3-field dissection was an independent predictor of a favorable outcome.[17] Similar results were found in the present study. However, in the analysis of groups D and E (i.e., after 2003), there was no difference in prognosis between the 2- and 3-field lymphadenectomy. The Cox proportional hazards analysis also did not identify lymphadenectomy as a prognostic factor. The contribution of prophylactic 3-field lymphadenectomy to prognosis is a subject of discussion.[38,39] The differences in patient backgrounds between groups D and E and groups A–C were an increase in the number of older patients and those with early-stage cancer. However, there was no significant difference in prognosis between 2- and 3-field lymphadenectomy, even when analyzing only patients aged <75 years or those with stage III/IV cancer (Supplemental Digital Content 1 and 2 http://links.lww.com/AOSO/A266, which are figures showing the analysis results).

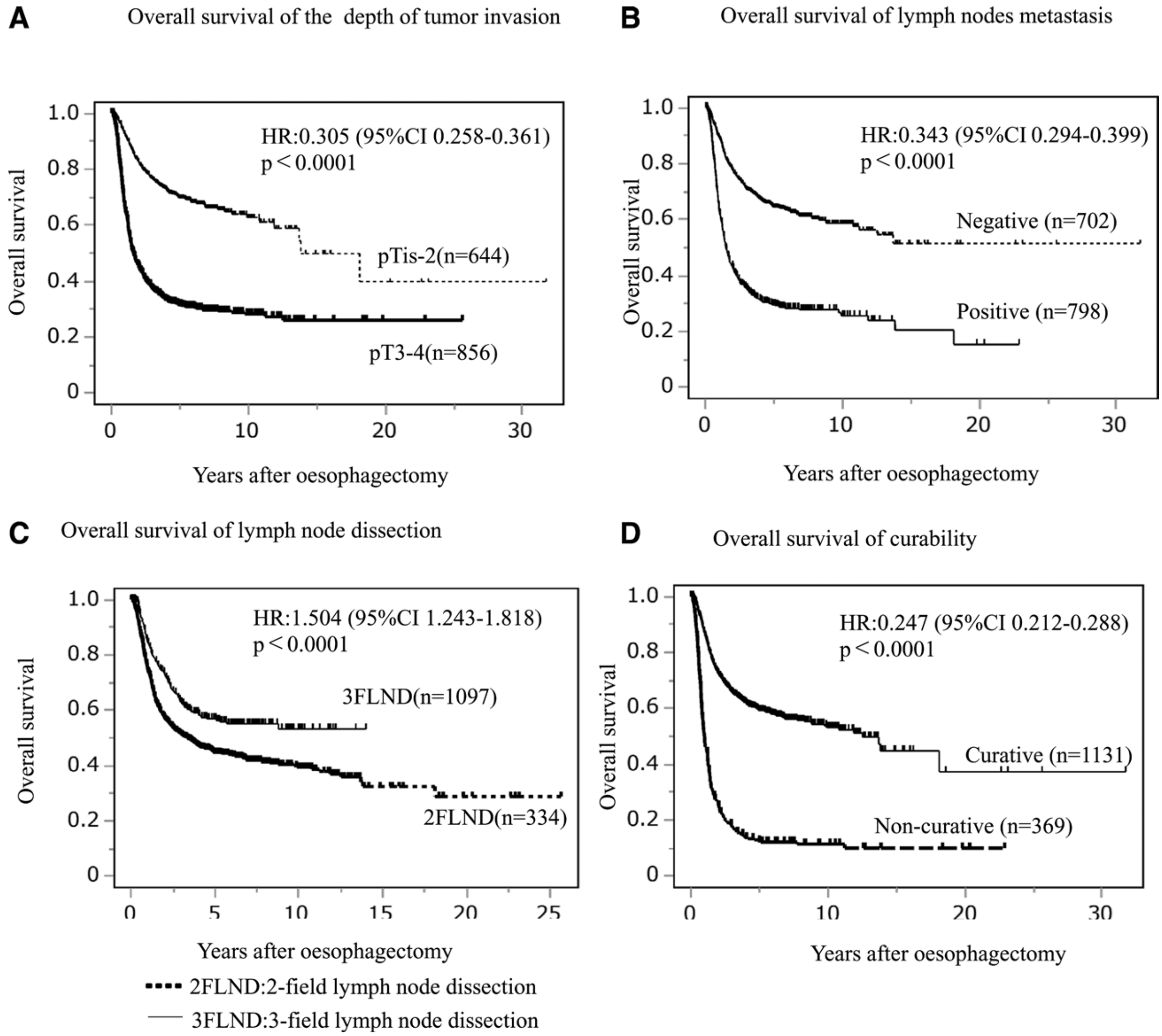



**FIGURE 2.** Overall survival on the basis of the prognostic factors of the 1500 consecutive patients with esophageal cancer. (A) Tumor depth of invasion (pTis–T2 or pT3,4) in accordance with the UICC eighth edition: The pTis–T2 group had a significantly better prognosis than the group pT3,4 (HR: 0.305, 95% CI: 0.258–0.361; $P < 0.0001$). (B) Lymph node metastasis (positive or negative) in accordance with the UICC eighth edition: group negative (pN0) had a significantly better prognosis than group positive (HR, 0.343; 95% CI: 0.294–0.399; $P < 0.0001$). (C) Extent of lymphadenectomy (2- or 3-field lymphadenectomy): 3-field lymphadenectomy was associated with a better prognosis than 2-field lymphadenectomy (HR: 1.504, 95 % CI: 1.243–1.818; $P < 0.0001$). (D) Curative resection (curative resection or noncurative resection): patients who underwent curative resection had a significantly better prognosis than those who underwent noncurative resection (HR: 0.247; 95% CI: 0.212–0.288; $P < 0.0001$). pTis, pathological tumor in situ; T2, tumor invading the muscularis propria; UICC, Union for International Cancer Control; HR, hazard ratio; CI, confidence interval.

Furthermore, improvements in perioperative treatment have an impact on prognosis, and survival is expected to improve with interventions, such as lymphadenectomy or chemoradiotherapy after recurrent cervical lymph node metastasis.[40] In groups D and E, the efficacy of extended lymphadenectomy was not considered to have a strong influence on prognosis, owing to various factors.

### *Changes in Chemotherapy*

Chemotherapy and chemoradiotherapy have changed dramatically over time. 5-fluorouracil and cisplatin were the mainstays of treatment until the 1990s, and in the 2000s, docetaxel and paclitaxel became available for the treatment of postoperative esophageal cancer recurrence. In 2020, ICIs were available for the treatment of recurrence and postoperative adjuvant therapy in Japan.[41–43] It is possible that changes in chemotherapy or ICIs as well as changes in surgery and patient background factors contribute to improved prognosis. Preoperative chemoradiotherapy has long been the standard treatment in Western countries. In our prior multivariate analysis of 1000 cases, we found that preoperative radiotherapy was an independent factor associated with pulmonary complications. Considering that the majority of esophageal cancer cases in Japan are located in the middle thoracic region, we believe that preoperative chemotherapy is a rational treatment approach.[13]

### *Limitations*

This study has some limitations. First, this was a single-institution retrospective study and unexpected bias could not be completely ruled out. However, the fact that standardized surgical strategies and techniques were used within the institution and the sample size was large are major advantages of this study. Additionally, the cases were consecutive, and TNM classification and complications were analyzed according to the latest

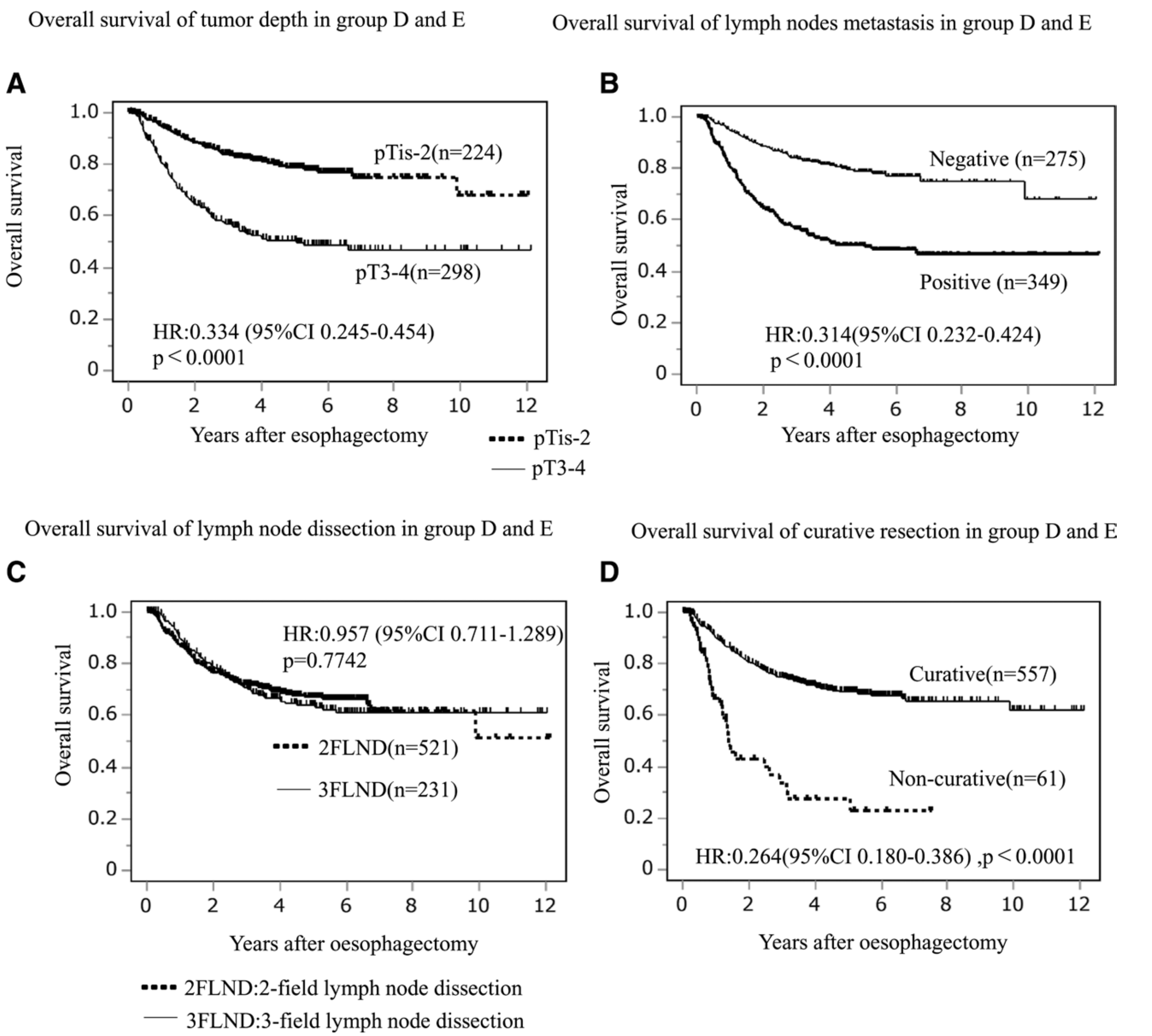



**FIGURE 3.** Overall survival on the basis of the prognostic factors in groups D and E. (A) Depth of tumor invasion (pTis–T2 or pT3,4) in accordance with the UICC eighth edition: The pTis–T2 group had a significantly better prognosis than that pT3,4 group (HR: 0.334, 95% CI: 0.245–0.454; $P < 0.0001$). (B) Lymph node metastasis (positive or negative) in accordance with the UICC eighth edition showed that the Negative group had a significantly better prognosis than the Positive group (HR: 0.314, 95% CI: 0.232–0.424); $P < 0.0001$). (C) Extent of lymphadenectomy (2- or 3-field lymphadenectomy): There was no significant difference between the 2- and 3-field lymphadenectomy. Univariate and multivariate Cox proportional analyses showed similar results (hazard ratio [HR]: 0.957; 95% confidence interval [CI]: 0.711–1.289; $P = 0.7742$). (D) Curative resection (curative resection or noncurative resection): Patients who underwent curative resection had a significantly better prognosis than those who underwent non-curative resection (HR: 0.264, 95% CI: 0.180–0.386; $P < 0.0001$). pTis, pathological tumor in situ; T2, Tumor invading the muscularis propria; UICC, Union for International Cancer Control; HR, hazard ratio; CI, confidence interval; pN0, pathological node stage zero.

criteria. Second, this study showed that certain prognostic factors are important. However, other factors, including other clinical parameters and patient comorbidities, have not been analyzed; therefore, more extensive information is needed to optimize disease management and treatment strategies.

## CONCLUSIONS

Esophageal cancer treatment has evolved over time, leading to changes in the treatment outcomes and prognostic factors. Because of the standardization of surgical techniques and an aging society, the focus has shifted from complications and 3-field dissection to tumor staging and curative resection. Curative resection is crucial in advanced cases. Standardization of treatment strategies, including preoperative chemotherapy, surgical techniques, and postoperative management, is essential to achieve curative resection without complications. The importance of multidisciplinary treatment has increased over time. Drug therapy is expected to play a role in future outcomes, with the approval of ICIs for adjuvant therapy and recurrent treatment. Nonetheless, the primary goal for surgeons in esophageal cancer is to achieve curative resection, and its importance remains universal.

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**TABLE 5.**

**Analysis of the Prognostic Factors Using Cox Proportional Hazard Analysis in Groups D and E**

| Factor | Object | Control | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|
| | | | Hazard Ratio (95% CI) | *P* | Hazard Ratio (95% CI) | *P* |
| Age (years) | <75 | ≥75 | 0.692 (0.460–1.023) | 0.065 | | |
| Sex | Male | Female | 1.137 (0.761–1.700) | 0.395 | | |
| Location of the tumor | Ce/Ut | Mt/Lt | 1.380 (1.015–1.877) | 0.039 | 1.293 (0.865–1.934) | 0.271 |
| Depth of invasion | T0/1/2 | T3/T4 | 0.334 (0.245–0.454) | <0.0001 | 0.421 (0.286–0.619) | <0.0001 |
| Lymph node metastasis | Negative | Positive | 0.314 (0.232–0.424) | <0.0001 | 0.381 (0.286–0.556) | <0.0001 |
| Extent of lymphadenectomy | 2-field | 3-field | 0.957 (0.711–1.289) | 0.774 | | |
| Resectability | R0 | R1 or R2 | 0.264 (0.180–0.386) | <0.0001 | 0.477 (0.316–0.721) | 0.0004 |
| Pulmonary complications | None | Present | 0.787 (0.468–1.161) | 0.189 | | |
| Anastomotic leakage | None | Present | 0.922 (0.624–1.363) | 0.687 | | |

CI, confidence interval; Ce, cervical; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; T, tumor.

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