Prognosis of Patients with Esophageal Carcinoma following Routine Thoracic Duct Resection: A Propensity-matched Analysis of 12,237 Patients based on the Comprehensive Registry of…

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Prognosis of patients with esophageal carcinoma following routine thoracic duct resection: A propensity-matched analysis of 12,237 patients based on the Comprehensive Registry of Esophageal Cancer in Japan

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Mini-abstract

This large-scale multicenter cohort study investigating 12,237 esophagectomies throughout Japan showed that thoracic duct resection did not improve prognosis after strict matching. The thoracic duct resection group had significantly more distant metastases compared to the preservation group. Indiscriminate thoracic duct resection should not be recommended for patients with esophageal cancer.

Each authors contribution to the manuscript

1. Dr. Oshikiri, Dr. Numasaki, Dr. Oguma, and Dr. Toh made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data
2. Dr. Watanabe, Dr. Muto, and Dr. Doki participated in drafting the article or revising it critically for important intellectual content
3. Dr. Kakeji gave final approval of the version to be published.

Abstract

Objective: To clarify whether routine thoracic duct (TD) resection improves the prognosis of patients with esophageal cancer after radical esophagectomy.

Summary Background Data: Although TD resection can cause nutritional disadvantage and immune suppression, it has been performed for the resection of surrounding lymph nodes.

Methods: We analyzed 12,237 patients from the Comprehensive Registry of Esophageal Cancer in Japan who underwent esophagectomy between 2007 and 2012. TD resection and preservation groups were compared in terms of prognosis, perioperative outcomes, and initial recurrent patterns using strict propensity score matching. Particularly, the year of esophagectomy and history of primary cancer of other organs were added as covariates.

Results: Following propensity score matching, 1638 c-Stage I–IV patients participated in each group. The five-year overall survival and cause-specific survival rates were 57.5% and 55.2% in the TD-resected group and 65.6% and 63.4% in the TD-preserved group, respectively, without significant differences. The TD-resected group had significantly more retrieved mediastinal nodes (30 vs. 21, $P < 0.0001$) and significantly fewer lymph node recurrence (376 vs. 450, $P = 0.0029$) compared with the TD-preserved group. However, the total number of distant metastatic organs was significantly greater in TD-resected group than in the TD-preserved group (499 vs. 421, $P = 0.0024$).

Conclusions: TD resection did not improve survival in patients with esophageal cancer. Despite having retrieved more lymph nodes, TD resection caused distant metastases in more organs compared to TD preservation. Hence, prophylactic TD resection should not be recommended in patients with esophageal cancer.

INTRODUCTION

Esophagectomy remains the primary approach for treating esophageal cancer, which has been one of the deadly malignant diseases worldwide due to its malignant potential.[1] One of the purposes of esophagectomy is to control regional lymph node (L/N) metastases via lymphadenectomy. Indeed, studies have highlighted the usefulness of removing a sufficient number of L/Ns to improve the prognosis of patients with esophageal cancer.[2,3]

Mediastinal L/Ns, which exist in the adipose tissue surrounding the thoracic duct (TD), has included in the regional L/Ns for thoracic esophageal cancer.[4,5] Thus, TD resection has been performed for the resection of surrounding L/Ns, thereby increasing the number of L/Ns retrieved.[6] However, whether TD resection really contributes to improving prognosis of esophageal cancer patients remains controversial. In fact, TD resection has been found to promote hemodynamic changes, increased pulse rate, and nutritional disadvantages in the immediate postoperative period.[7,8] Although several reports have discussed whether TD resection is necessary[9,10] or not[11,12] during esophagectomy for esophageal cancer, such studies were not well adjusted or had an insufficient amount of patients to determine the necessity of TD resection.

Studies using a retrospective cohort of patients from multiple centers need to minimize selection bias. Adjusting for confounding factors should be done appropriately to evaluate the effectiveness of surgical interventions. Propensity score matching (PSM) is one of commonly used approaches for minimizing selection bias.[13] However, PSM without a sufficient subset of confounders has been used inappropriately in some studies, leading to incorrect conclusions.

The Comprehensive Registry of Esophageal Cancer in Japan (CRECJ) is a large database of Japan Esophageal Society. The characteristics of this unique database include both precise short-term outcomes and long-term survival data. Using this large cohort database with quite strict PSM, the current study aimed to clarify whether routine TD resection improves long-term outcome of esophageal cancer patients treated with esophagectomy.

METHODS

Data collection

This multi-central, propensity-matched analysis investigated esophageal cancer patients treated with esophagectomy with or without TD resection in Japan. The CRECJ is a national data management system that continuously and comprehensively collects the perioperative and long-term outcomes of patients with esophageal cancer. From 2007 to 2012, 21,952 esophageal cancer patients treated with surgical procedures were registered at the CREJC. From this population, patients treated with esophagectomy and satisfied the criteria were included.

All patients were diagnosed using computed tomography, esophagogastroduodenoscopy, ultrasonography, endoscopic ultrasonography, esophagography, and positron emission tomography at each institution. The seventh edition of the Union for International Cancer Control tumor node metastasis cancer staging system was used to diagnose esophageal cancer.[14] Eligibility criteria for participating this study were as follows: (1) age 80 years or younger; (2) primary tumor located in the thoracic esophagus; (3) histologically proven esophageal squamous cell carcinoma (ESCC) or adenocarcinoma (AC); (4) esophagectomy with thoracotomy including thoracoscopic procedure via right thoracic cavity; and (5) cT1-3, cN0-3, and cM0-1 disease (cM1 is limited to only supraclavicular lymph nodes metastases). Salvage operations, including esophagectomies after definitive chemoradiation (dCRT) or esophagectomies with neoadjuvant chemotherapy (NACRT), were excluded given that neoadjuvant chemotherapy (NAC) is the standard treatment in Japan.[15] Records of patients who refused to publish their information or those with missing data were also excluded.

Finally, among the patients enrolled in the CRECJ between 2007 and 2012, a total of 12,237 patients treated with esophagectomy in 326 hospitals were eligible for inclusion (Figure. 1).

Endpoints

The primary outcomes were overall survival (OS) and cause-specific survival (CSS). The secondary outcomes were initial recurrence patterns, the number of retrieved nodes, and the status of circumferential resection margin. As subgroup analyses using PSM, outcomes in patients with c-stage IA (cT1N0M0) and c-Stage II–IV (cT2-3/N1-3/M0-1) were evaluated. This study protocol was approved by the Institutional Review Boards at all the participating hospitals in the CRECJ project.

Statistical Analysis

In this cohort study, PSM was used to gather two comparable 1:1 groups, selecting sex, age, year of esophagectomy, tumor location, histology, tumor depth (cT), lymph node metastasis (cN), preoperative chemotherapy, thoracic procedure (open or thoracoscopy), lymph node dissection, and multi cancer of other organs as covariates. A caliper of width of 0.20 standard deviation of the estimated logit was used.

Subgroup analyses of survival in patients with c-stage IA and II–IV were also done using PSM as mentioned above.

To estimate the differences in categorical variables between the two groups, χ^2 test was used. Concerning the continuous variables, Mann–Whitney U test or Student's t-test were used, as appropriate. Survival curves were evaluated and compared by the Kaplan–Meier method and log-rank test. All statistical analyses were performed with SAS 9.4 (SAS Institute, Salty, NC, USA), with *P* values less than 0.05 indicating statistical significance.

RESULTS

Patients

c-Stage I-IV (cT1-3/N0-3/M0-1) patients

In total, 12,237 patients with thoracic esophageal cancer were included in this study

(Figure 1), a third of whom (4,040 patients) were treated with thoracoscopic esophagectomy. The TD-resected and -preserved group contained 1,815 and 10,422 patients, respectively. Demographic and clinical characteristics of patients with c-Stage I-IV are summarized in Table 1. Patients were matched into the both groups each containing 1,638 patients based on the propensity score (Figure 1). Although significant differences in baseline characteristics, age, year of esophagectomy, tumor location, cT, cN, c-Stage, preoperative chemotherapy, thoracic procedure, and lymph node dissection were observed before adjusting, all were eliminated after PSM (Table 1).

c-Stage IA (cT1N0M0) patients

The total number of patients with c-stage IA included was 3,306. The TD-resected and -preserved groups contained 291 and 3,015 patients, respectively. Using the PSM applying same covariates other than cT, patients were matched into both groups, with each group containing 273 patients. Although significant differences were observed in baseline characteristics before adjustment, all were eliminated after PSM (Supplemental table 1).

c-Stage II–IV (cT2-3/N1-3/M0-1) patients

The total number of patients with c-stage II–IV included was 5,288. The TD-resected and–presented groups contained 1,023 and 4,265 patients, respectively. After PSM, 914 patients were ultimately selected for each group. Although significant differences were observed in baseline characteristics before adjustment, all were eliminated after PSM (Supplemental table 2).

Survival, number of retrieved mediastinal nodes, and status of circumferential resection margin

c-Stage I-IV (cT1-3/N0-3/M0-1) patients

Across all stages, OS and CSS rates were evaluated. OS rates in the TD-resected group were 84.1%, 70.5%, 63.5%, 60.8%, and 57.5% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. OS rates in the TD-preserved group were 85.3%, 71.8%, 63.8%, 58.7%, and 55.2% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2A). CSS rates in the TD-resected group were 87.3%, 75.5%, 70.0%, 67.7%, and 65.6% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. CSS rates in the TD-preserved group were 89.0%, 76.4%, 69.6%, 65.1%, and 63.4% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2B). Median survival periods were 53 (0–83) months and 51 (0–82) months in TD-resected and -preserved groups, respectively. There was no significant difference in the OS and CSS curves between the TD-resected and -preserved groups (Figure 2A; $P = 0.367$, Figure 2B; $P = 0.307$). After evaluating surgical outcomes, we found that the TD-resected group had significantly more retrieved mediastinal nodes compared to the TD-preserved group (30 vs. 21, $P < 0.0001$). No significant differences in circumferential resection margin negative status were observed between both groups (93% vs. 94%, P = 0.379).

c-Stage IA (cT1N0M0) patients

Among c-Stage IA stage, OS rates in the TD-resected group were 94.8%, 90.3%, 85.4%, 84.2%, and 82.0% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. OS rates in the TD-preserved group were 96.3%, 91.7%, 87.0%, 82.2%, and 80.1% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2C). CSS rates in the TD-resected group were 99.2%, 96.8%, 94.0%, 93.1%, and 92.1% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. CSS rates in the TD-preserved group were 98.8%, 96.9%, 95.6%, 92.5%, and 91.1% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2D). Median survival periods were 54 (0–79) months and 53 (1–82) months in TD-resected and -preserved groups, respectively. No significant intergroup differences in the OS and CSS curves were noted (Figure 2C; $P = 0.552$, Figure 2D; $P = 0.746$). The TD-resected group had significantly more retrieved mediastinal nodes compared to the TD-preserved group (30 vs. 21, $P < 0.0001$). No significant differences in circumferential resection margin negative status were noted between both groups (99% vs. 99%, $P = 0.704$).

c-Stage II–IV (cT2-3/N1-3/M0-1) patients

Among c-Stage II–IV stages, OS rates in the TD-resected group were 78.5%, 61.0%, 53.4%, 49.9%, and 46.4% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. OS rate in the TD-preserved group were 80.2%, 62.3%, 52.0%, 46.9%, and 44.5% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2E). CSS rates in the TD-resected group were 80.5%, 65.1%, 58.9%, 55.7%, and 53.2% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively. CSS rates in the TD-preserved group were 84.1%, 66.7%, 57.9%, 53.3%, and 51.6% at the 1st, 2nd, 3rd, 4th, and 5th year, respectively (Figure 2F). Median survival periods were 36 (0–81) months and 33 (0–82) months in TD-resected and -preserved groups, respectively. No significant differences in the OS and CSS curves were observed between the TD-resected and -preserved groups (Figure 2E; $P = 0.606$, Figure 2F; $P = 0.793$). The TD-resected group had significantly more retrieved mediastinal nodes compared to the TD-preserved group (30 vs. 20, $P < 0.0001$). No significant differences in circumferential resection margin negative status were observed between both groups (89% vs. 91%, $P = 0.374$).

Initial recurrence patterns in TD-resected or preserved patients

c-Stage I-IV (cT1-3/N0-3/M0-1) patients

Patterns of postoperative recurrence are detailed in Table 2. The TD-resected group had significantly fewer lymph node recurrences compared to the TD-preserved group (376 vs. 450, $P = 0.0029$). Although the TD-resected group had less local recurrence compared to the TD-preserved group, no significant difference was seen (55 vs. 76, $P = 0.061$). The TD-resected group had significantly more total number of distant metastatic organs compared to the TD-preserved group (499 vs. 421, $P = 0.0024$) (Table 2).

c-Stage IA (cT1N0M0) patients

No significant differences in the location of recurrence [lymph nodes (21 vs. 26, P = 0.446), local area near the primary tumor (0 vs. 3, P = 0.082)] and total number of distant metastatic organs (17 vs. 26, P = 0.157) were seen between both groups.

c-Stage II–IV (cT2-3/N1-3/M0-1) patients

The TD-resected group had fewer lymph node (273 vs. 312, P=0.051) and local (47 vs. 66, P = 0.065) recurrence compared to the TD-preserved group, although there was no significant difference. The TD-resected group had significantly more total number of distant metastatic organs compared to the TD-preserved group (379 vs. 307, P = 0.0005).

Characteristics of distant metastatic group

c-Stage I–IV (cT1-3/N0-3/M0-1) patients

The number of cN2/3 patients was significantly higher in the distant metastatic group than in the group without distant metastasis (38% vs. 20%, P < 0.0001 in the TD-resected group; 33% vs. 22%, P < 0.0001 in the TD-preserved group).

Subgroup analysis

Figure 3 shows the forest plot of the HRs for OS in patients with c-Stage I–IV (cT1-3/N0-3/M0-1). Between both groups, no significant difference in each subgroup was seen (Figure 3).

DISCUSSION

The current study found no superiority of TD resection in primary outcomes (i.e., OS and CSS) across various populations in comparison to TD preservation. On the other hand, TD resection contributed to the retrieval of more lymph nodes. A previous report similarly showed that the TD resection had promoted the retrieval of significant more mediastinal nodes compared to the TD-preserved group (27.9 vs. 20.0).[6] As such, lymph nodes recurrences were lower in TD-resected group in comparison to the TD-preserved group significantly among c-Stage I–IV and c-Stage II–IV populations. Concerning the local status, the TD-resected group only tended to have fewer recurrences, with no significant differences have been observed. This suggests that TD resection promotes better control of metastatic lymph nodes and can guarantee sufficient surgical margin.

However, among the c-Stage I–IV and c-Stage II–IV populations, TD-resected group had a significantly higher total number of distant metastatic organs compared to TD-preserved group. Similarly, Oshikiri et al. also described that the TD-resected group promoted significantly more distant bone metastases in their propensity score-matched study.[9] The aforementioned results indicate that immunological hypofunction due to TD resection might cause systemic metastases. To induce humoral immunity, B and T cell interactions are critical. Moreover, T follicular helper (Tfh) cells in germinal centers of secondary lymphoid organs are pivotal for these interactions. Vella et al. proved that a subset of cTfh cells originate from the lymph nodes and traffic into the blood via the TD.[16] Tfh cells exit from the lymph nodes into the blood as circulating Tfh cells to suppress micrometastases. Conversely, TD resection affects the tumor immune microenvironment and can facilitate immune escape of microcancer cells. Thus, the advantage of TD resection in controlling lymph node metastases is negated by its disadvantage of suppressing immunity, consequently promoting no improvement in prognosis. Although some populations might benefit from TD resection, indiscriminate TD resection for cT3N3 or lower-grade patients should be avoided based on these results. In Western countries, neoadjuvant chemoradiotherapy (NACRT) is more popular than neoadjuvant chemotherapy (NAC) for esophageal cancer. Recently, population-based cohort study showed that NACRT promoted better survival compared to NAC for ESCC. Moreover, NACRT is advantageous given its ability to secure margin status.[17] Thus, Western patients with ESCC receiving NACRT can also avoid TD resection.

Consequently, TD resection is recommended for bulky tumors which are suspected to invade TD directly. In those cases, certain tumor excision with negative surgical margin is expected by TD resection. For patients with clinical L/N metastases around the TD, TD resection is also beneficial to control metastatic lesions, leading to less local recurrence. On the contrary, TD resection should be avoided for patients at risk of immune suppression, particularly accounting for factors such as, advanced age, malnutrition, sarcopenia, etc. that correspond to immune suppression status.[18–20] In addition, TD should be preserved for patients with high risk of systemic metastasis. In this high risk population, preservation of immune strength is crucial to prevent systemic recurrence after esophagectomy. Based on our data, not a few clinical L/Ns metastases (cN2/3) is a risk factor for systemic metastasis.

During PSM analyses, a small subset of confounders can lead to incorrect conclusions. Notably, some differences in esophageal cancer treatment were observed according to the treatment period at which neoadjuvant therapy was introduced and the thoracic procedure (i.e., open thoracotomy or minimally invasive procedures). Thus, in our matched cohort of 12,237 patients, we added yearly treatment period, NAC, and thoracic procedure to the covariates in order to avoid treatment period bias. Moreover, in esophageal cancer patients, the high incidence rate of multiple cancers originated in other organs is worth noting.[21,22] Of course, these cancers of other organs also greatly affect survival. Thus, it is quite important to select multiple cancers of other organs as covariates for adequate PSM. In Japan, based on national clinical database (NCD), around 5,000–6,000 esophageal cancer patients were treated with esophagectomy annually.[23,24] Hence, nearly 80% of esophagectomies in Japan were registered to the CRECJ from more than 300 participating hospitals.[25] The characteristic feature of CRECJ is that it possesses survival data, which is lacking in the NCD. Consequently, CRECJ is a unique Japanese national database that contains survival data, which allows quite strict

PSM for survival analyses. These are outstanding characteristics of the present study that make it stand out from the rest.

Some limitations of our study warrant discussion. First, this is a retrospective cohort study. Additionally, the CRECJ lacks data on perioperative complications and the date of recurrence due to the characteristics of its registry system. Thus, analyses of complications with or without TD resection and disease-free survival could not be done. To estimate these outcomes, randomized control studies are required.

Conclusion

TD resection did not improve survival in various subgroups of patients with esophageal cancer. Although TD resection contributed to increasing the total amount of retrieved lymph nodes, leading to less lymph nodes recurrence, TD-resected group had a significantly higher total number of distant metastatic organs than the TD-preserved group. Consequently, indiscriminate TD resection should not be recommended for esophageal cancer patients.

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Figure legends

Fig. 1

Flowchart of patient enrollment for c-Stage I–IV (cT1-3/N0-3/M0-1) patients.

Fig. 2

A) Among c-Stage I–IV patients, the OS rates in the group TD-resected (1,638 patients) at the 1st, 2nd, 3rd, 4th, and 5th year were 84.1%, 70.5%, 63.5%, 60.8%, and 57.5% and 85.3%, whereas those in TD-preserved group (1,638 patients) were 71.8%, 63.8%, 58.7%, and 55.2%, respectively (P = 0.367).

B) Among c-Stage I–IV patients, the CSS rates in the TD-resected group (1,638 patients) at the 1st, 2nd, 3rd, 4th, and 5th year were 87.3%, 75.5%, 70.0%, 67.7%, and 65.6%, whereas those in the TD-preserved group (1,638 patients) were 89.0%, 76.4%, 69.6%, 65.1%, and 63.4%, respectively (P = 0.307).

C) Among c-Stage IA patients, the OS rates in TD-resected group (273 patients) for of at the 1st, 2nd, 3rd, 4th, and 5th year were 94.8%, 90.3%, 85.4%, 84.2%, and 82.0%, whereas those in the TD-preserved group (273 patients) were 96.3%, 91.7%, 87.0%, 82.2%, and 80.1%, respectively (P = 0.552).

D) Among c-Stage IA patients, the CSS rates in in TD-resected group (273 patients) at the 1st, 2nd, 3rd, 4th, and 5th year were 99.2%, 96.8%, 94.0%, 93.1%, and 92.1%, whereas those in the TD-preserved group (273 patients) were 98.8%, 96.9%, 95.6%, 92.5%, and 91.1%, respectively (P = 0.746).

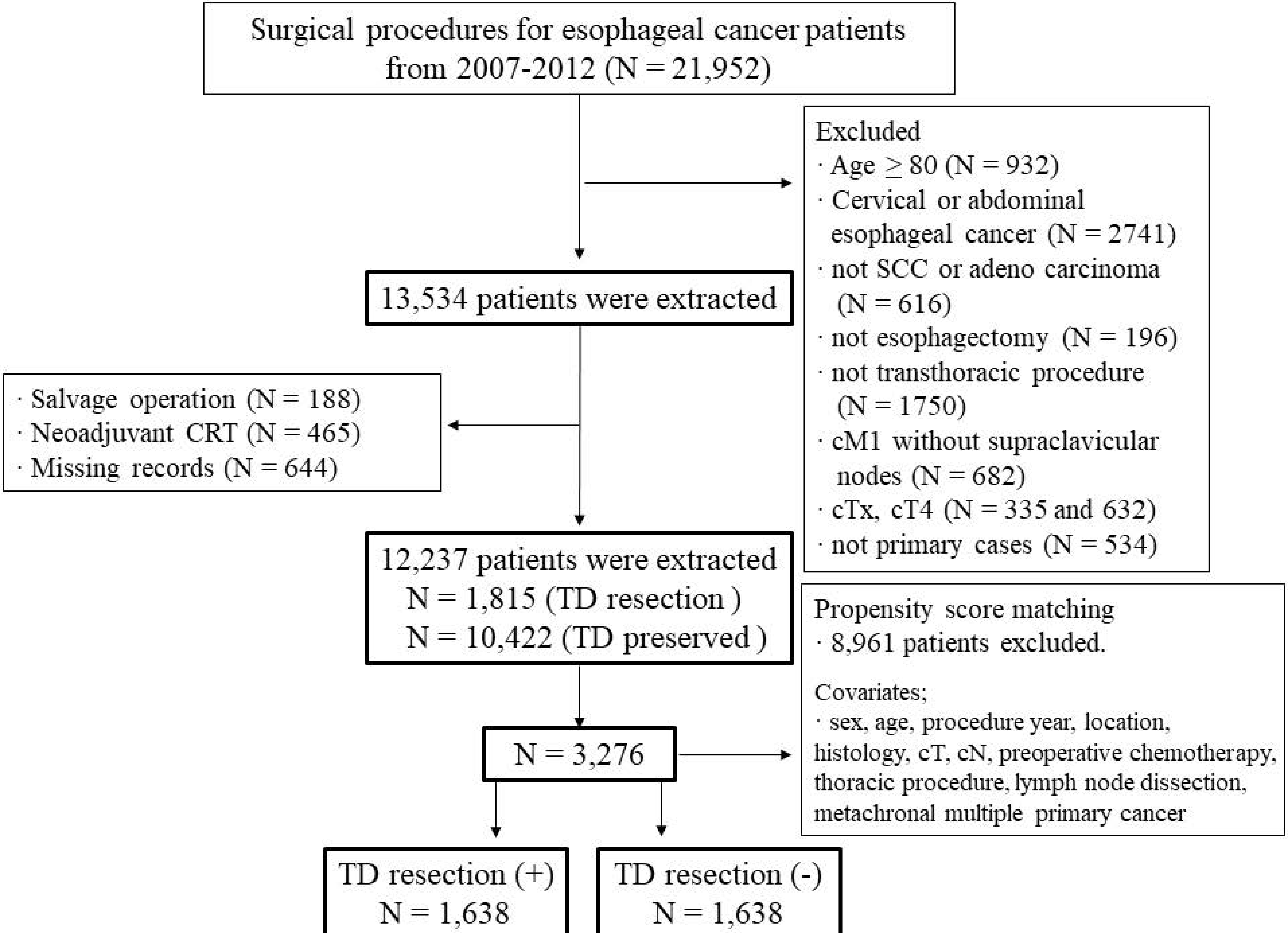
E) Among c-Stage II–IV patients, the OS rates in the TD-resected group (914 patients) at the 1st, 2nd, 3rd, 4th, and 5th year were 78.5%, 61.0%, 53.4%, 49.9%, and 46.4%, whereas those for in the TD-preserved group (914 patients) were 80.2%, 62.3%, 52.0%, 46.9%, and 44.5%, respectively (P = 0.606).

F) Among of c-Stage II–IV patients, the CSS rates in the TD-resected group (914 patients) at the 1st, 2nd, 3rd, 4th, and 5th year were 80.5%, 65.1%, 58.9%, 55.7%, and 53.2%, whereas those in the TD-preserved group (914 patients) were 84.1%, 66.7%, 57.9%, 53.3%, and 51.6%, respectively ($P = 0.793$).

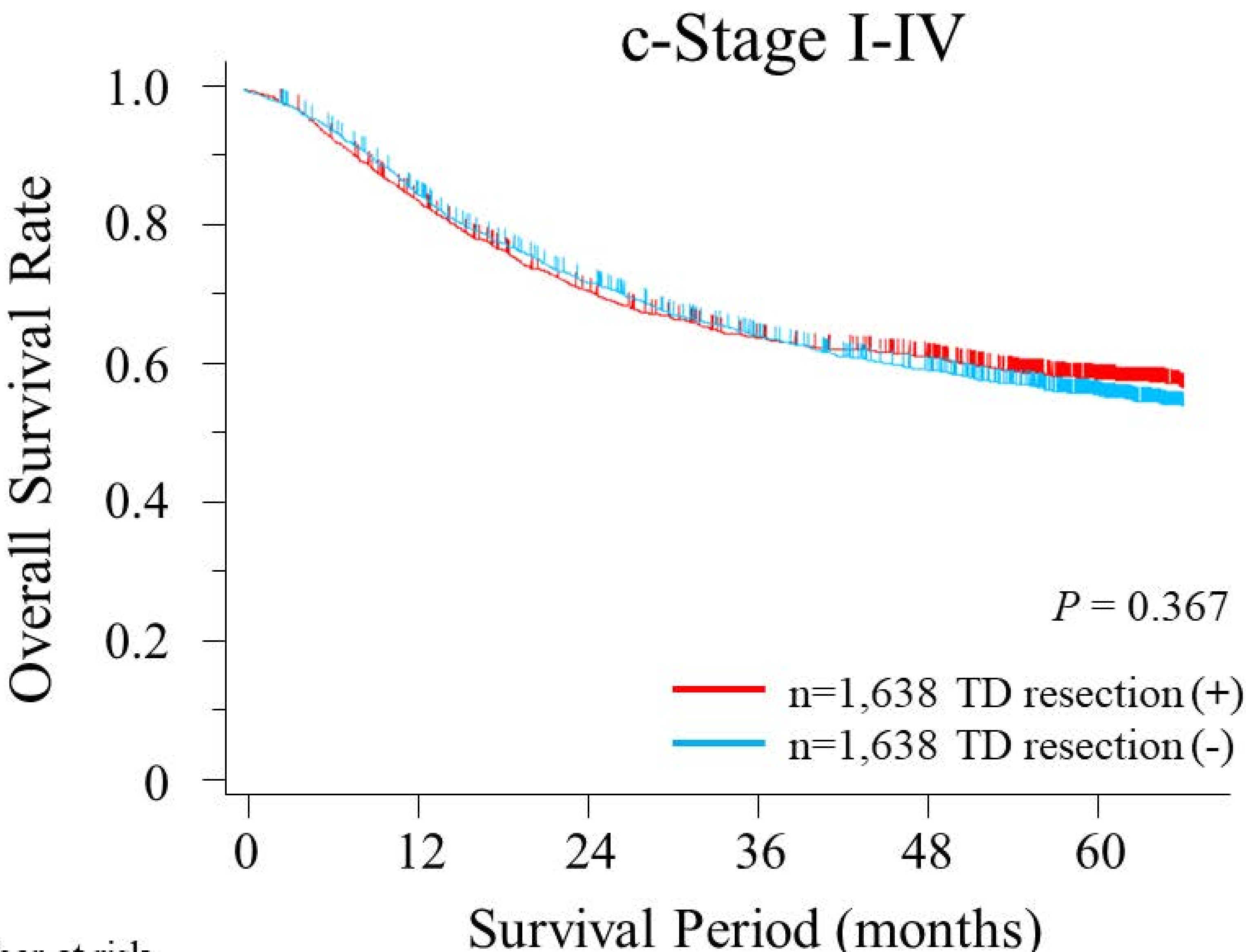
c-Stage, clinical stage; OS, overall survival; CSS, cause-specific survival; TD, thoracic duct.

Fig. 3

The forest plot of hazard ratios for overall survival in c-Stage I–IV (cT1-3/N0-3/M0-1) patients showed no significant difference between both groups in all subgroups.

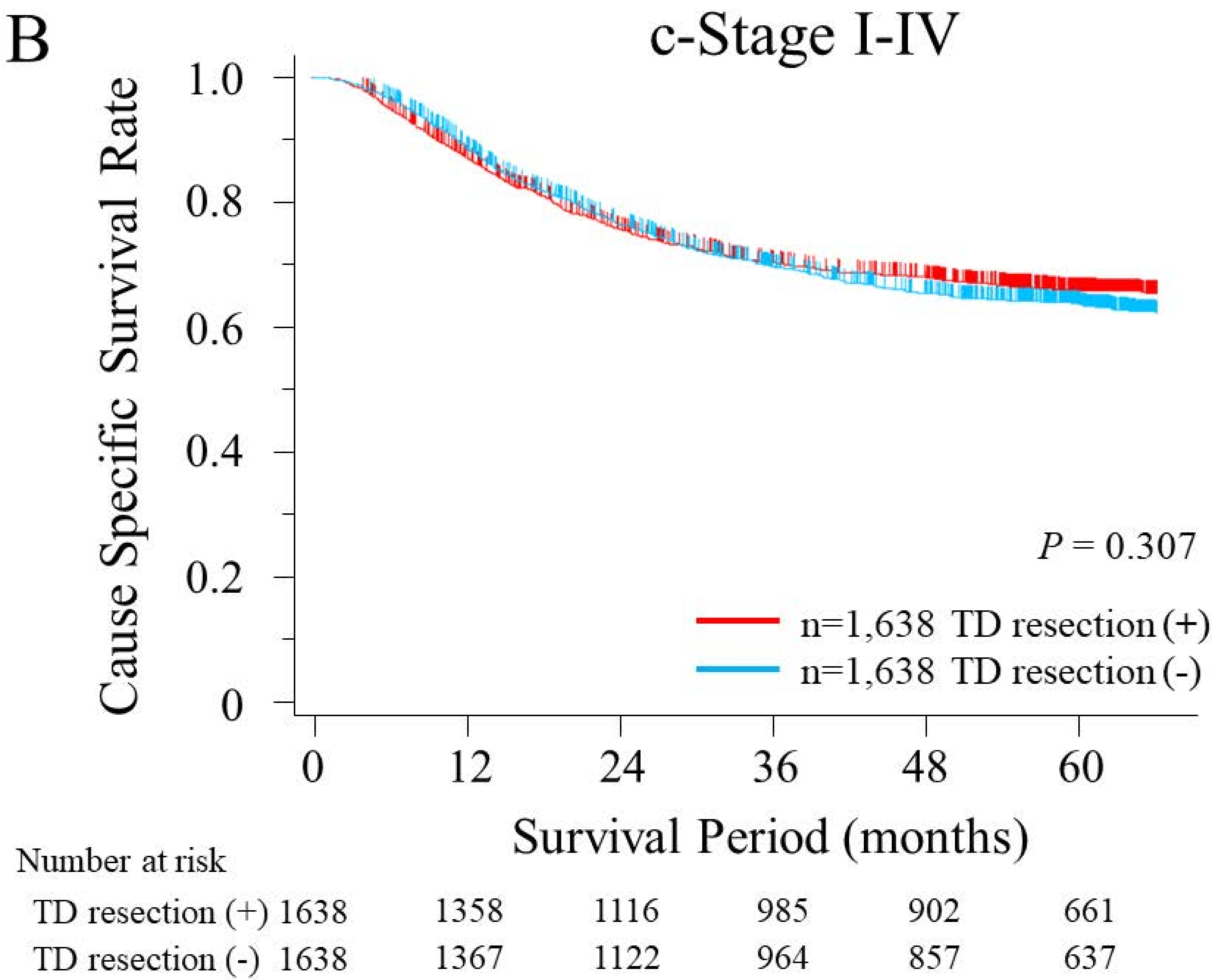

Surgical procedures for esophageal cancer patients from 2007-2012 (N = 21,952)
Excluded
· Age ≥ 80 (N = 932)
· Cervical or abdominal esophageal cancer (N = 2741)
· not SCC or adeno carcinoma (N = 616)
· not esophagectomy (N = 196)
· not transthoracic procedure (N = 1750)
· cM1 without supraclavicular nodes (N = 682)
· cTx, cT4 (N = 335 and 632)
· not primary cases (N = 534)
13,534 patients were extracted
· Salvage operation (N = 188)
· Neoadjuvant CRT (N = 465)
· Missing records (N = 644)
12,237 patients were extracted
N = 1,815 (TD resection)
N = 10,422 (TD preserved)
Propensity score matching
· 8,961 patients excluded.
Covariates;
· sex, age, procedure year, location, histology, cT, cN, preoperative chemotherapy, thoracic procedure, lymph node dissection, metachronal multiple primary cancer
N = 3,276
TD resection (+)
N = 1,638
TD resection (-)
N = 1,638

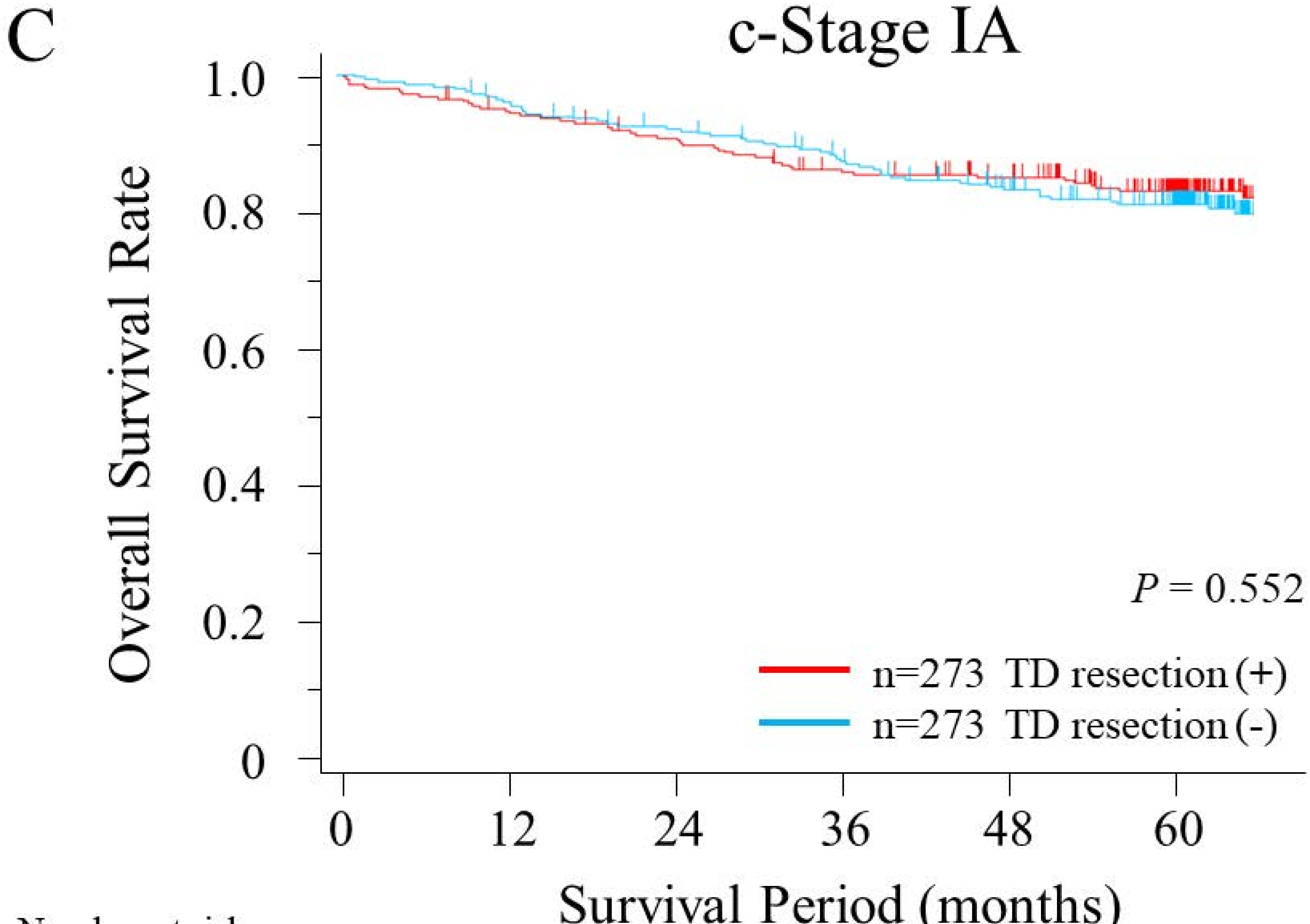
A



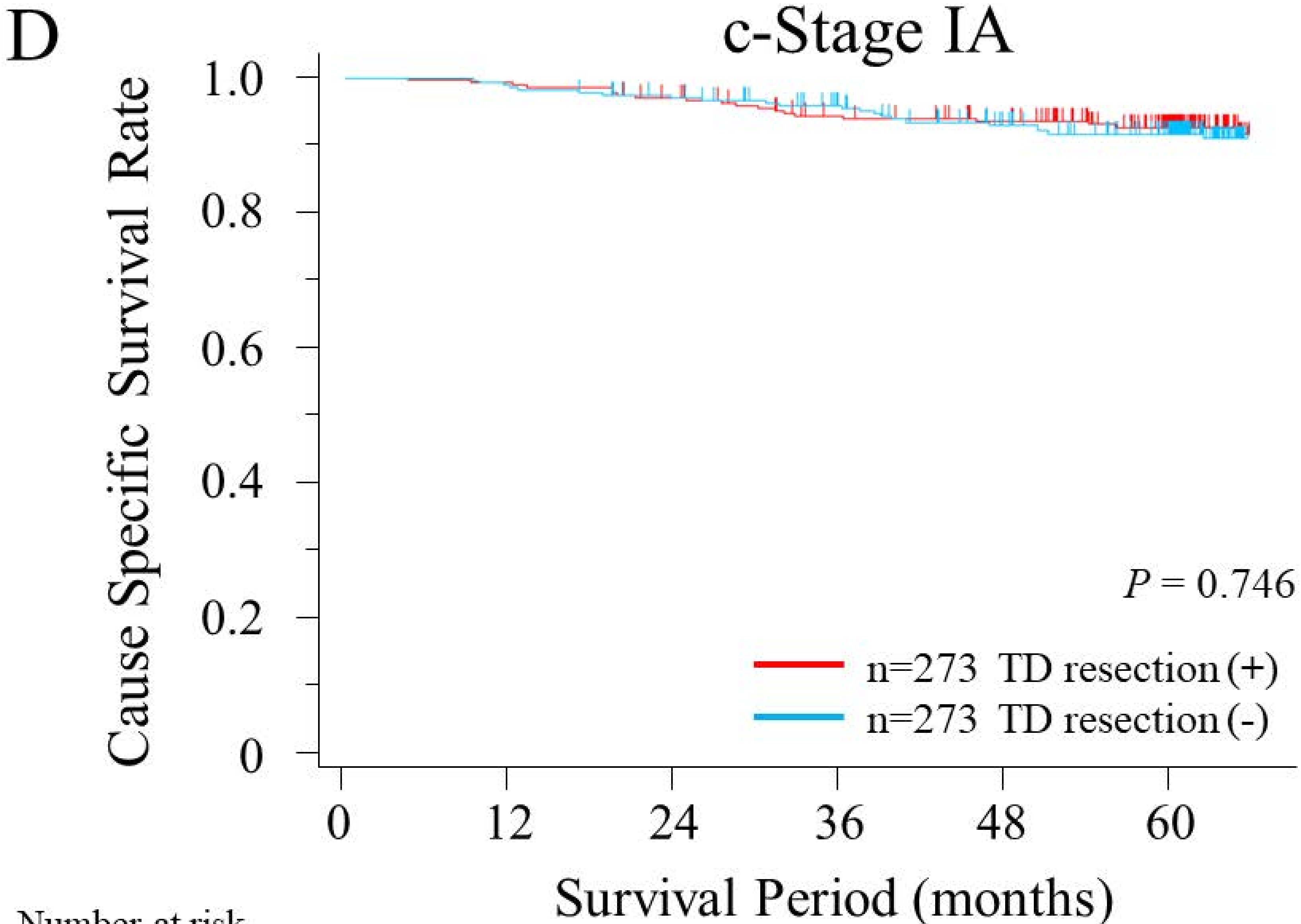
Number at risk

	0	12	24	36	48	60
TD resection (+)	1638	1358	1116	985	902	661
TD resection (-)	1638	1367	1122	964	857	637


B
c-Stage I-IV
Cause Specific Survival Rate
1.0
0.8
0.6
0.4
0.2
0
P = 0.307
n=1,638 TD resection (+)
n=1,638 TD resection (-)
0
12
24
36
48
60
Survival Period (months)
Number at risk
TD resection (+) 1638 1358 1116 985 902 661
TD resection (-) 1638 1367 1122 964 857 637

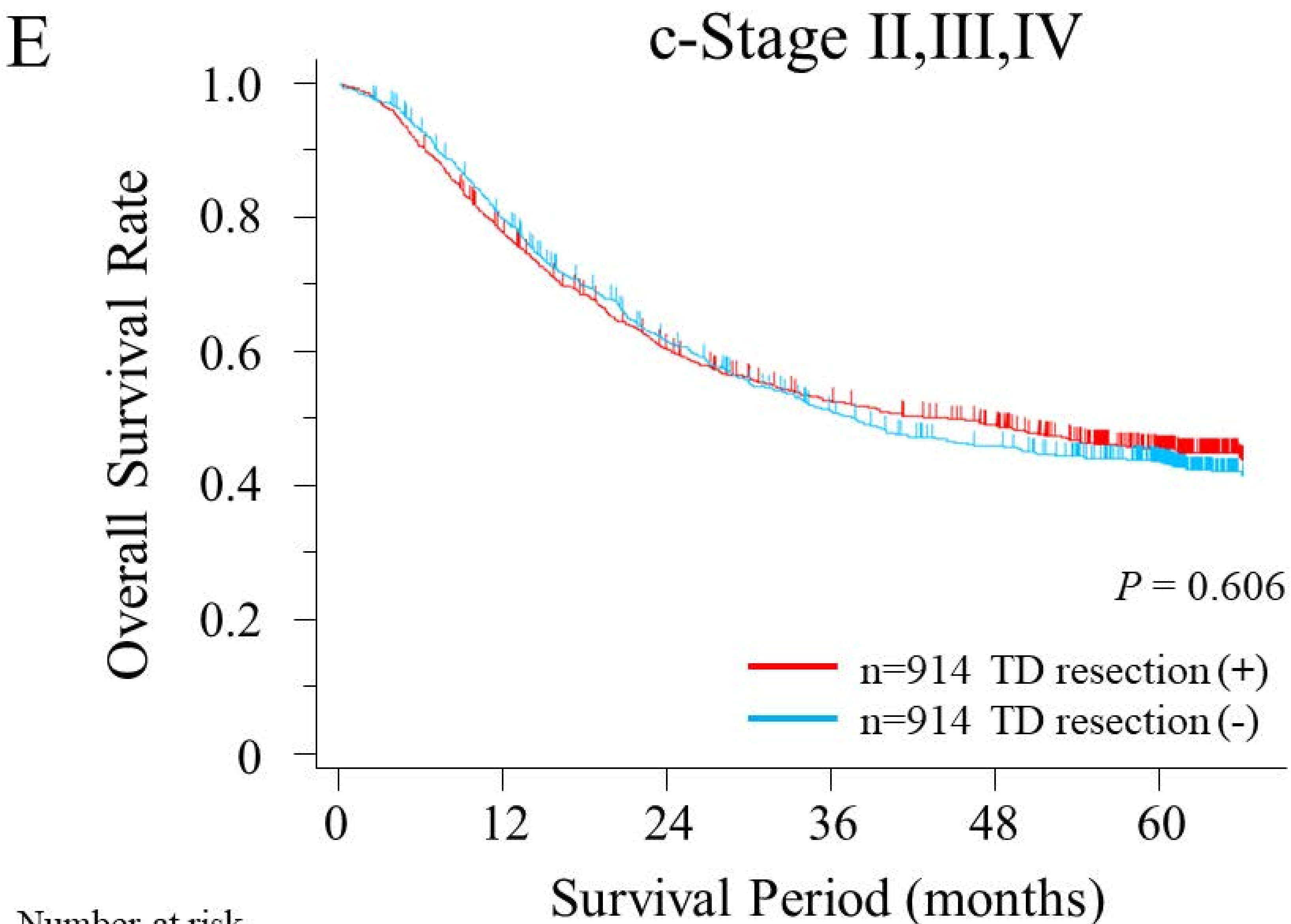


Number at risk						
TD resection (+)	273	253	239	222	211	162
TD resection (-)	273	254	238	221	199	168



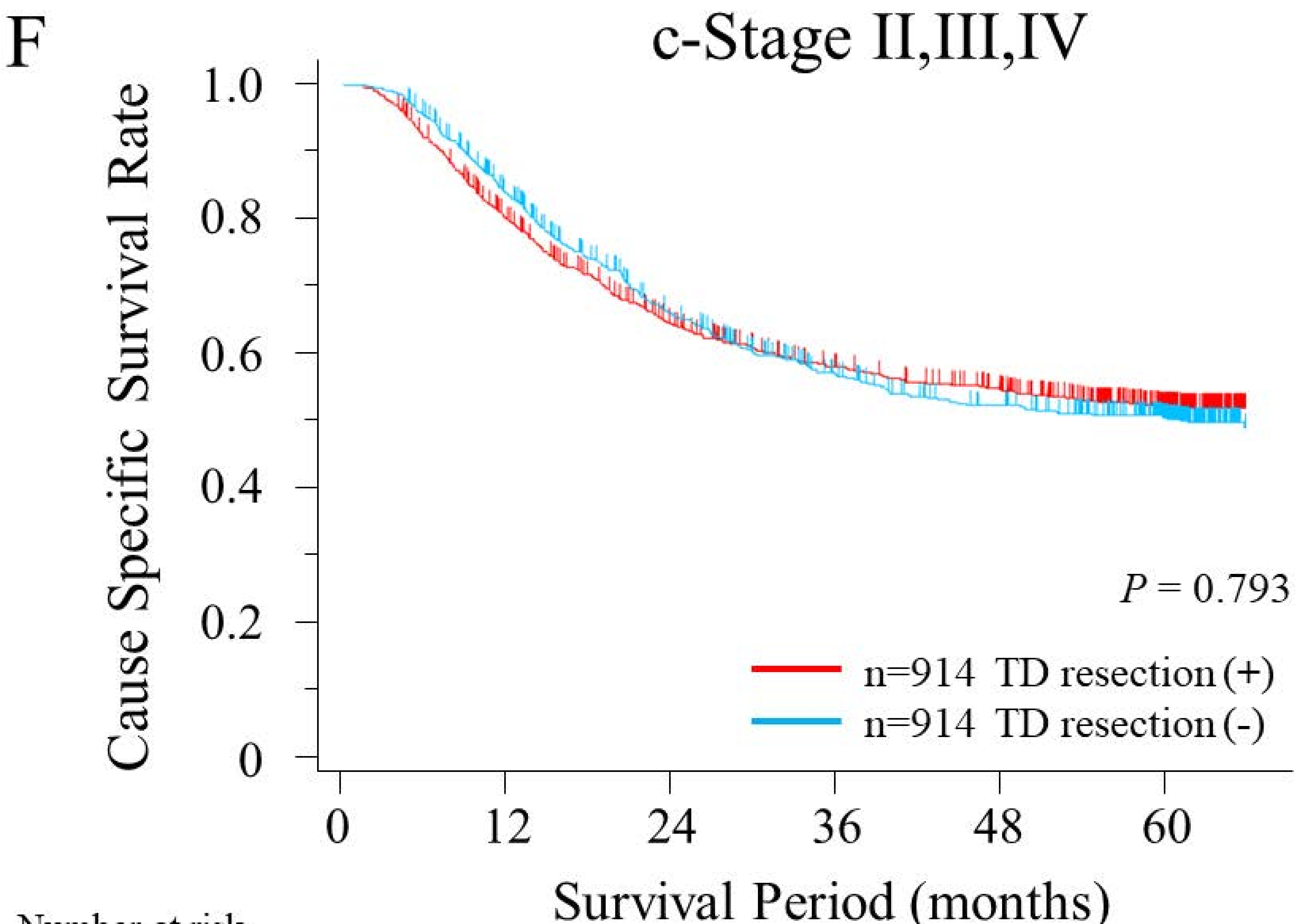
Number at risk

TD resection (+)	273	253	239	222	211	162
TD resection (-)	273	254	238	221	199	168



Number at risk

TD resection (+)	914	704	536	456	410	294
TD resection (-)	914	716	538	433	378	291



Number at risk

	0	12	24	36	48	60
TD resection (+)	914	704	536	456	410	294
TD resection (-)	914	716	538	433	378	291

Subgroup		TD resection/ TD preservation	HR	95% CI	p-value
Gender	Male	1409/1440	0.95	0.85 - 1.06	0.315
	Female	229/198	1.09	0.78 - 1.51	0.624
Year of the esophagectomy	2007	225/236	0.93	0.71 - 1.22	0.603
	2008	197/186	0.75	0.55 - 1.02	0.062
	2009	301/299	0.92	0.71 - 1.18	0.488
	2010	313/307	1.05	0.82 - 1.35	0.705
	2011	266/266	0.90	0.70 - 1.16	0.413
	2012	336/344	1.12	0.89 - 1.41	0.337
Tumor location	Upper	179/163	0.86	0.63 - 1.18	0.346
	Middle	933/943	0.95	0.82 - 1.09	0.444
	Lower	526/532	0.99	0.83 - 1.20	0.943
Histology	Scc	1605/1609	0.95	0.85 - 1.05	0.314
	Adeno carcinoma	33/29	1.16	0.57 - 2.34	0.689
Depth of tumor invasion	cT1	412/408	0.97	0.72 - 1.32	0.865
	cT2	317/313	0.98	0.77 - 1.24	0.839
	cT3	909/917	0.94	0.83 - 1.07	0.354
Lymph node metastasis	cN0	575/565	0.98	0.79 - 1.21	0.823
	cN1	652/666	0.91	0.77 - 1.07	0.251
	cN2	318/318	0.96	0.78 - 1.18	0.711
	cN3	73/75	1.27	0.86 - 1.86	0.228
Distant metastases	cM0	1622/1629	0.95	0.86 - 1.06	0.363
	cM1	16/9	1.04	0.31 - 3.56	0.947
Preoperative chemotherapy	Yes	653/667	1.05	0.89 - 1.22	0.585
	No	985/971	0.90	0.78 - 1.03	0.124
Thoracic procedure	Thoracoscopy	415/433	0.90	0.73 - 1.12	0.356
	Open thoracotomy	1223/1205	0.97	0.86 - 1.09	0.565
Lymph node dissection	Two-field	472/484	1.04	0.86 - 1.26	0.700
	Three-field	1166/1154	0.92	0.81 - 1.04	0.172
Multiple cancer of other organs	Yes	133/118	1.03	0.71 - 1.48	0.894
	No	1505/1520	0.95	0.85 - 1.06	0.327

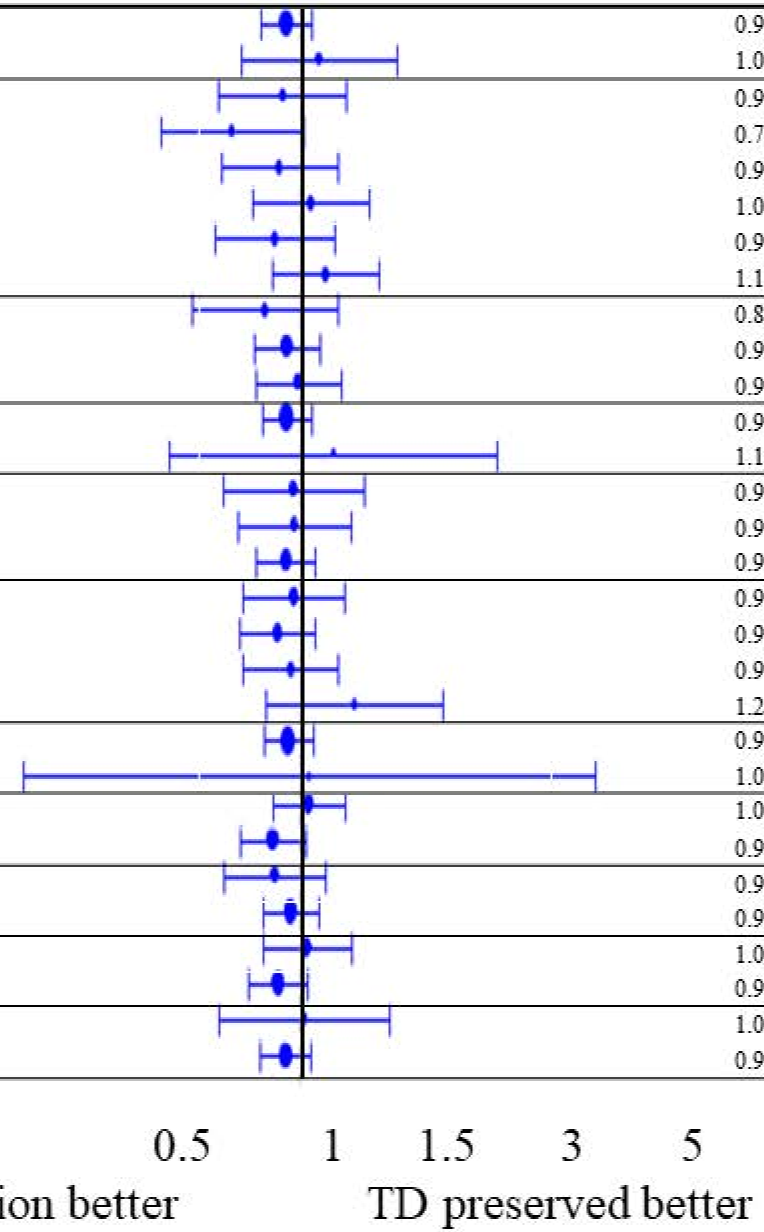


Table 1. Demographic and clinical characteristics of c-Stage I-IV patients

	Patients of c-Stage I-IV (cT1-3/N0-3/M0-1)					
	Entire cohort			Matched cohort		
	Patients with TD resection (*n* = 1815)	Patients with TD preservation (*n* = 10422)	*P*	Patients with TD resection (*n* = 1638)	Patients with TD preservation (*n* = 1638)	*P*
Gender (male/female)	1552/249 (86%/14%)	8848/1562 (85%/15%)	0.194 [a]	1409/229 (86%/14%)	1440/198 (88%/12%)	0.108 [a]
Age (years)	65 (32-79)	66 (27-79)	0.0002 [b]	65 (32-79)	65 (27-79)	0.942 [b]
Year			0.0002 [a]			
2007	252 (14%)	1220 (12%)		225 (14%)	236 (14%)	0.981 [a]
2008	209 (12%)	1206 (12%)		197 (12%)	186 (12%)	
2009	318 (18%)	1890 (18%)		301 (18%)	299 (18%)	
2010	351 (19%)	1708 (16%)		313 (19%)	307 (19%)	
2011	296 (16%)	2060 (20%)		266 (16%)	266 (16%)	
2012	389 (21%)	2338 (22%)		336 (21%)	344 (21%)	
Tumor location (upper/middle/lower)	204/1047/564 (11%/58%/31%)	1381/5676/3365 (13%/55%/32%)	0.015 [a]	179/933/526 (11%/57%/32%)	163/943/532 (10%/58%/32%)	0.658 [a]
Histology (SCC/adeno carcinoma)	1778/37 (98%/2%)	10245/177 (98%/2%)	0.308 [a]	1605/33 (98%/2%)	1609/29 (98%/2%)	0.608 [a]
Depth of tumor invasion (cT1a/1b/2/3)	52/392/347/1024 (3%/22%/19%/56%)	587/3269/2111/4455 (6%/31%/20%/43%)	<.0001 [a]	50/362/317/909 (3%/22%/19%/56%)	45/363/313/917 (3%/22%/19%/56%)	0.955 [a]
Lymph node metastasis (cN 0/1/2/3)	650/732/357/76 (36%/40%/20%/4%)	5365/3184/1579/294 (51%/31%/15%/3%)	<.0001 [a]	595/652/318 (36%/40%/19%/5%)	579/666/318/75 (35%/41%/19%/5%)	0.858 [a]
Distant metastases (cM 0/1)	1799/16 (99%/1%)	10367/55 (99%/1%)	0.067 [a]	1622/16 (99%/1%)	1629/9 (99%/1%)	0.160 [a]
UICC c-stage (I/II/III/IV)	531/283/871/16 (31%/17%/51%/1%)	4655/1546/3690/55 (47%/16%/37%/1%)	<.0001 [a]	483/258/776/16 (32%/17%/51%/1%)	487/237/846/9 (31%/15%/54%/1%)	0.157 [a]
Preoperative chemotherapy (yes/no)	733/1068 (41%/59%)	3782/6550 (37%/63%)	0.0009 [a]	653/985 (40%/60%)	667/971 (41%/59%)	0.608 [a]
Thoracic procedure (thoracoscopy/open)	435/1325 (25%/75%)	3605/6549 (35%/65%)	<.0001 [a]	415/1223 (25%/75%)	433/1205 (26%/74%)	0.473 [a]
Lymph node dissection (two-field/three-field)	491/1221 (29%/71%)	3982/5078 (44%/56%)	<.0001 [a]	472/1166 (29%/71%)	484/1154 (29%/71%)	0.645 [a]
Multiple cancer of other organs (yes/no)	150/1659 (8%/92%)	944/9448 (9%/91%)	0.277 [a]	133/1505 (8%/92%)	118/1520 (7%/93%)	0.325 [a]

TD; thoracic duct

[a] χ^2 test

[b] Student's t-test

Table 2. Initial recurrence patterns in patients with thoracic duct resection or preservation of c-Stage I-IV patients

	Patients of c-Stage I-IV (cT1-3/N0-3/M0-1)					
	Entire cohort			Matched cohort		
	Patients with TD resection (*n* = 1815)	Patients with TD preservation (*n* = 10422)	*P*	Patients with TD resection (*n* = 1638)	Patients with TD preservation (*n* = 1638)	*P*
Lymph nodes	430	2454	0.893	376	450	0.0029 [a]
Local (area near the primary tumor)	65	399	0.611	55	76	0.061 [a]
Distant	554	2488	< 0.001 [a]	499	421	0.0024 [a]
Dissemination	88	334	0.001	79	57	0.054 [a]
Lung	157	780	0.085	140	139	0.950 [a]
Liver	134	636	0.038	119	93	0.065 [a]
Bone	87	413	0.099	81	73	0.509 [a]
Brain	25	102	0.122	24	19	0.443 [a]
others	63	223	0.001	56	40	0.097 [a]

[a] χ^2 test , TD; thoracic duct