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A Substudy of The Dutch Nationwide Ivory Study

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Objective: This study investigated the patterns, predictors, and survival of recurrent disease following esophageal cancer surgery.

Background: Survival of recurrent esophageal cancer is usually poor, with limited prospects of remission.

Methods: This nationwide cohort study included patients with distal esophageal and gastroesophageal junction adenocarcinoma and squamous cell carcinoma after curatively intended esophagectomy in 2007 to 2016 (follow-up until January 2020). Patients with distant metastases detected

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during surgery were excluded. Univariable and multivariable logistic regression were used to identify predictors of recurrent disease. Multivariable Cox regression was used to determine the association of recurrence site and treatment intent with postrecurrence survival.

Results: Among 4626 patients, 45.1% developed recurrent disease a median of 11 months postoperative, of whom most had solely distant metastases (59.8%). Disease recurrences were most frequently hepatic (26.2%) or pulmonary (25.1%). Factors significantly associated with disease recurrence included young age (≤65 y), male sex, adenocarcinoma, open surgery, transthoracic esophagectomy, nonradical resection, higher T-stage, and tumor positive lymph nodes. Overall, median postrecurrence survival was 4 months [95% confidence interval (95% CI): 3.6–4.4]. After curatively intended recurrence treatment, median survival was 20 months (95% CI: 16.4–23.7). Survival was more favorable after locoregional compared with distant recurrence (hazard ratio: 0.74, 95% CI: 0.65–0.84).

Conclusions: This study provides important prognostic information assisting in the surveillance and counseling of patients after curatively intended esophageal cancer surgery. Nearly half the patients developed recurrent disease, with limited prospects of survival. The risk of recurrence was higher in patients with a higher tumor stage, nonradical resection and positive lymph node harvest.

Keywords: esophageal cancer, esophagectomy, neoadjuvant treatment, palliative treatment, recurrences

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With over half a million cases annually, esophageal cancer is the seventh commonest malignancy in the world.[1] Overall, 5-year survival rates approximate only 22%.[2] An esophageal resection, through either a transthoracic or transhiatal procedure, combined with neoadjuvant chemo(radio)therapy is the cornerstone of curative treatment, after which 5-year survival rates increase to 51%.[3,4]

In recent years, the introduction of minimally invasive surgery has led to decreased postoperative morbidity and neoadjuvant chemoradiotherapy has improved survival.[5,6] Despite these significant improvements in treatment regimens and clinical outcomes, esophageal cancer recurrence remains a frequent observation. Currently, approximately half of all patients develop recurrent disease after esophageal cancer surgery.[7,8] The survival is usually poor, and the prospects of remission are limited.[9] Prognosis is not only influenced by the available (palliative) treatment options, but also by the site of disease recurrence.[10,11]

There is little information in the scientific literature concerning the recurrence patterns after esophagectomy, their predictors and prognostic consequences. Previous studies were predominantly performed before the implementation of minimally invasive esophagectomy and neoadjuvant chemoradiotherapy, and their results were equivocal.[12–14] The aim of the current study was to investigate the patterns of esophageal cancer recurrence after esophagectomy with curative intent in a large nationwide cohort. In addition, the predictors and survival of recurrent esophageal cancer were examined.

METHODS

This study was a post hoc analysis of the IVORY study,[15] a retrospective nationwide cohort study evaluating the trends in care and postoperative outcomes for patients with distal esophageal and gastroesophageal junction cancer. All 23 hospitals providing surgical esophageal cancer care in the Netherlands in 2007 to 2016 participated in the IVORY study, and approval from the Institutional Review Boards of every participating center was obtained. According to Dutch law, no informed consent or ethical approval was required as data were anonymized. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines to ensure correct reporting of study methods and results[16] (Supplemental Digital Content 1, http://links.lww.com/SLA/E104).

Patients

Patients who underwent a transthoracic or transhiatal esophagectomy with gastric conduit reconstruction between January 2007 and December 2016 were eligible. Only elective esophagectomies performed with curative intent for distal esophageal or gastroesophageal junction adenocarcinoma or squamous cell carcinoma were included. Patients referred for salvage surgery, with intraoperative distant metastasis (n = 54, 1.1%), with unknown recurrence status (n = 32, 0.7%), and who did not agree with the anonymous use of their data were excluded.

Outcomes

Primary outcome measures were the rate and site of disease recurrence after curatively intended esophageal cancer surgery. The clinicopathological predictors of disease recurrence, and the postrecurrence survival for the different sites (locoregional, distant) and treatment intents (none, palliative, curative) of recurrent disease were also investigated. Survival was defined as the interval from first diagnosis of disease recurrence to death or last follow-up. Follow-up on survival status and disease recurrence was collected until January 2020, guaranteeing a minimum follow-up of 3 years.

Treatment and Follow-up

In general, neoadjuvant treatment consisted of chemoradiotherapy according to the CROSS scheme, or perioperative chemotherapy (MAGIC scheme) for patients with more gastric involvement. Patients in poor physical condition, or with early-stage cancer (cT1) did not receive multimodal treatment.[5,17] The type of esophageal resection and extent of lymphadenectomy were determined by surgeon preferences and could be adjusted according to preoperative tumor characteristics and lymph node status, although a complete 3-field lymphadenectomy was not routine practice.

Follow-up protocols are standardized in the Netherlands.[18] Generally, postoperative outpatient visits were scheduled every 3 months during the first year, every 6 months from the second to fourth year, and once in the fifth year.[18] A positron emission tomography (PET) computed tomography (CT) scan and/or endoscopy with biopsy was performed when recurrent disease was suspected.[3,19] Clinical symptoms raising the suspicion of recurrent disease include dysphagia, fatigue, and lymphadenopathy.

Definitions and Locations of Recurrence

Disease recurrences were classified as solely locoregional, solely distant, or combined. Locoregional recurrences were located at the site of the primary tumor or in the locoregional lymph nodes, distant recurrences were located systemic or in nonregional lymph nodes, and combined recurrences were defined as the coexistence of locoregional and distant recurrences, regardless of the order of occurrence. Organ system or anatomically closely related recurrence sites were combined into bridging groups (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/SLA/E105), which were stratified by tumor histology and surgical procedure. Treatment intent for disease recurrence was divided into curative, palliative, or none (ie, best supportive care), as generally discussed during multidisciplinary team meetings. R0 resections were defined as

no gross or microscopic tumor remains in the luminal and circumferential resection margins.

Statistical Analysis

Variables were compared using independent t, 1-way analysis of variance, Kruskal-Wallis H, Mann-Whitney U, or χ^2 tests when appropriate, and outcomes were reported accordingly as either the mean ± SD, median with interquartile range (IQR) or numbers with corresponding percentages.

To identify factors associated with disease recurrence, univariable, and multivariable logistic regression analyses were performed. Both preoperative and postoperative variables were included to predict disease recurrence more closely. On the basis of literature and baseline characteristics, age, sex, tumor location, histology, clinical and pathological tumor and node stage, (response to) neoadjuvant treatment, surgical approach and procedure, lymph node harvest and surgical radicality were included. Following univariable logistic regression, variables with a P-value <0.2 were excluded by backward selection during multivariable logistic regression until only statistically significant variables remained in the model.[20,21] The multivariable regression model was tested for multicollinearity and interaction terms, which were not present between the included variables. Outcomes were presented as odds ratios (OR) with 95% confidence intervals (CI).

Unadjusted survival was analyzed using Kaplan-Meier estimates and log-rank tests. To determine the association of recurrence site (locoregional, distant) and treatment intent (curative, palliative, best supportive care) with postrecurrence survival adjusted for confounders, multivariable Cox regression analyses were performed. Potential confounders were included in the multivariable Cox model [age, sex, body mass index, American Society of Anesthesiologists (ASA) score, clinical stage, histology, tumor location, neoadjuvant treatment, surgical approach, procedure, and year] and outcomes were presented as hazard ratios (HR) with 95% CI.

Study data were entered and stored into an online Castor EDC database (ISO 27001 and NEN 7510 certified). Few missing data were present in primary analyses and were therefore handled by complete case analysis. Statistical analyses were performed with IBM Corp, Armonk, New York version 26.0. For all analyses, a 2-sided P-value of <0.05 was considered statistically significant.

RESULTS

Of 4626 patients included, the mean age at surgery was 64.6 years (SD: 9.2) and the majority were male (80.6%; in the Supplementary Table 4, Supplemental Digital Content 2, http://links.lww.com/SLA/E105). Most patients were diagnosed with an adenocarcinoma (87.1%), a cT3 tumor (73.5%), and with clinically suspected lymph nodes (62.9%). The neoadjuvant treatment rate was 84.2%, of whom 10.8% received chemotherapy and 89.2% chemoradiotherapy.

Patients With Recurrent Disease

During follow-up, 2088 patients (45.1%) developed recurrent disease, predominantly within the first postoperative year (median 11 mo, IQR: 6–21). Patients with recurrent disease were younger (63.9 vs. 65.2 y, $P<0.001$), more often had an adenocarcinoma (90.0% vs. 84.6%, $P<0.001$), a higher clinical T-stage (cT3: 80.0% vs. 68.1%, $P<0.001$), and a nonradical resection (8.5% vs. 3.3%, $P<0.001$). Fewer recurrences were observed after neoadjuvant chemoradiotherapy compared with chemotherapy (45.2% vs. 51.3%, $P=0.018$).

Patterns of Recurrent Disease

The site of recurrence was known in 98.6% of the 2088 patients, of whom 16.4% had locoregional recurrences, 59.8% had distant recurrences, and 23.9% had both. Locoregional recurrences most frequently occurred at the anastomosis or gastric conduit (16.5%), among whom the nonradical resection rate was high (15.2% vs. 7.2% for patients with recurrence elsewhere, $P<0.001$). Distant recurrences were most often hepatic (26.2%) or pulmonary (25.1%). Site of recurrent disease, also stratified by tumor histology, is presented in Table 1. The distribution of recurrent disease was comparable for squamous cell and adenocarcinomas (locoregional 22.0% vs. 15.8%; distant 56.1% vs. 60.2%; combined 22.0% vs. 24.1%; $P=0.075$).

Following neoadjuvant chemoradiotherapy, the number of locoregional recurrences (13.8%) was lower and the number of distant recurrences (63.9%) was higher than after chemotherapy (19.3% and 50.7%, respectively; $P=0.001$); the remaining 22.3% and 30.0% of each group had combined locoregional and distant recurrences.

The respective recurrence rates after transthoracic and transhiatal esophagectomy were comparable (46.0% vs. 43.9%, $P=0.175$) and exhibited a similar distribution (locoregional 16.0% vs. 16.9%; distant 59.7% vs. 59.8%; combined 24.2% vs. 23.3%; $P=0.809$). Site of recurrent esophageal cancer stratified by surgical procedure is shown in Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/SLA/E105.

Predictors of Esophageal Cancer Recurrence

Multivariable logistic regression (Table 2) revealed that age ≤65 years (OR: 1.27, 95% CI: 1.12–1.45), male sex (OR: 1.23, 95% CI: 1.04–1.46), open surgery (OR: 1.15, 95% CI: 1.00–1.33), positive pathological N stage (OR: 1.25, 95% CI: 1.21–1.30), and nonradical resection (OR: 1.36, 95% CI: 1.02–1.83) were associated with recurrent disease after esophagectomy, while squamous cell carcinoma (OR: 0.73, 95% CI: 0.59–0.89) and transhiatal procedure (OR: 0.83, 95% CI: 0.72–0.96) were inversely associated with disease recurrence. With the exception of pT1 tumors, there was an increasing association between higher clinical and pathological T stages and disease recurrence.

Treatment of Disease Recurrence

Treatment intent for disease recurrence was available for 1824 of 2088 patients (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/SLA/E105), of whom 6.9% had curative intent, 51.3% palliative intent, and 41.8% best supportive care. Patients who received treatment with curative intent were younger, had a lower ASA score, more R0 resections, lower pathological T and N stages, more often had locoregional recurrences, and had longer time to recurrence. The majority of patients with early recurrences (ie, within the first postoperative year) received treatment with palliative intent or best supportive care.

Postrecurrence Survival

Overall, the median postrecurrence survival was 4 months (95% CI: 3.64–4.36), 7 months in case of locoregional recurrence (95% CI: 5.65–8.35), 3 months for distant recurrence (95% CI: 2.56–3.44), and 4 months for combined recurrences (95% CI: 3.41–4.59) ($P<0.001$; Fig. 1). Adjusted survival was superior for patients with locoregional compared with distant recurrences (HR: 0.74, 95% CI: 0.65–0.84).

Without treatment, the median postrecurrence survival was 1 month (95% CI: 0.86–1.14), which was 7 months after treatment with palliative intent (95% CI: 6.42–7.58), and 20 months after treatment with curative intent (95% CI: 16.35–23.65) ($P<0.001$; Fig. 2). The adjusted survival of

TABLE 1. Site of Recurrent Esophageal Cancer After Esophagectomy With Curative Intent, Stratified by Tumor Histology

Site of Recurrence*	All Patients With Recurrent Disease, n = 2088, n (%)	Adenocarcinoma Recurrent Disease, n = 1880, n (%)	Squamous Cell Carcinoma Recurrent Disease, n = 208, n (%)
Locoregional	828 (40.3)	738 (39.5)	90 (44.0)
Anastomosis and gastric conduit	345 (16.5)	304 (16.2)	41 (19.7)
Diaphragm and pericardium	16 (0.8)	13 (0.7)	3 (1.4)
Cervical lymph nodes	165 (7.9)	143 (7.6)	22 (10.6)
Locoregional thoracic lymph nodes	318 (15.2)	289 (15.4)	29 (13.9)
Locoregional abdominal lymph nodes	107 (5.1)	97 (5.2)	10 (4.8)
Distant	1721 (83.7)	1561 (84.3)	160 (78.1)
Adrenal gland	119 (5.7)	113 (6.0)	6 (2.9)
Bone and bone marrow	432 (20.7)	397 (21.1)	35 (16.8)
Brain	195 (9.3)	180 (9.6)	15 (7.2)
Head and neck	13 (0.6)	13 (0.7)	0
Intestines	16 (0.8)	15 (0.8)	1 (0.5)
Liver and bile ducts	548 (26.2)	484 (25.7)	64 (30.8)
Lung	525 (25.1)	461 (24.5)	64 (30.8)
Muscle and (sub)cutis	154 (7.4)	137 (7.3)	17 (8.2)
Omentum and peritoneum	230 (11.0)	223 (11.9)	7 (3.4)
Pancreas	15 (0.7)	15 (0.8)	0
Pleural	242 (11.6)	220 (11.7)	22 (10.6)
Spleen	16 (0.8)	14 (0.7)	2 (1.0)
Urogenital	29 (1.4)	21 (1.1)	8 (3.8)
Distant lymph nodes	214 (10.2)	195 (10.4)	19 (9.1)
Other			
Recurrence in lymph nodes (NS)	152 (7.3)	137 (7.3)	15 (7.2)
Recurrence location unknown	67 (3.2)	63 (3.4)	4 (1.9)

*Multiple recurrence sites can apply to 1 patient.
NS indicates not further specified.

patients who received treatment with palliative intent (HR: 0.37, 95% CI: 0.33–0.41) and curative intent (HR: 0.23, 95% CI: 0.18–0.29) was superior to those who did not receive treatment.

Long-term remission was observed in a highly selected group of patients; 20 patients surpassed 5 years of follow-up (1.0% of 2088 patients), and another 43 patients surpassed 3 years of follow-up after first recurrence diagnosis (2.1%), with comparable time to recurrence to the overall patient group (12 mo, IQR: 7–21 vs. 11 mo, IQR: 6–21).

DISCUSSION

While most studies on esophageal cancer surgery focus on the primary setting, this nationwide cohort study investigated the patterns, predictors, and survival of esophageal cancer recurrence following esophagectomy with curative intent. Almost half of the patients developed recurrent disease, predominantly in the first postoperative year. Recurrences were mostly located distant, with liver and lungs the most frequently affected sites. Among others, higher T-stage, nonradical resection, and tumor positive lymph nodes were associated with disease recurrence. Post-recurrence survival was poor, especially for patients with distant metastasis, and patients treated without curative intent.

This study confirms the aggressive nature of esophageal cancer with high recurrence rates after curative treatment.[7,22–24] Variation in previously reported recurrence rates (38%–52%) may be due to differences in applied treatment regimens,[25] but may also be a result of variance in postoperative surveillance. In the participating centers, outpatient visits were scheduled regularly during the first 5 postoperative years, and (PET) CT scan and/or endoscopy were performed only when indicated, as recommended by the National Comprehensive Cancer Network and European Society for Medical Oncology Guidelines.[3,19] However, in several centers outside the Netherlands, active surveillance programs with routine imaging and/or endoscopy are implemented. The value of active surveillance is still a matter of debate, although it seems to be limited for surveillance endoscopy alone.[23,26,27] Patients with locoregional or oligometastatic recurrences eligible for curative treatment might benefit from routine imaging. However, based on current study results, we were not able to identify these patients yet and more studies are needed to support routine imaging for selected patients.

Most recurrences were observed at distant sites, which is in conformity with literature.[22,23,25] This might be due to the beneficial effect of increasingly used neoadjuvant chemoradiotherapy on locoregional tumor control, resulting in more R0 resections and fewer locoregional recurrences.[25,28,29] Although this might indicate a preference for neoadjuvant chemoradiotherapy, the results of the Neo-AEGIS trial comparing CROSS and perioperative chemotherapy are still awaited[30] and the indication for the specific therapy may differ. Perioperative chemotherapy may be chosen for cancers with more gastric involvement or a too extensive radiation field. In the case of residual pathological disease following neoadjuvant chemoradiotherapy and esophagectomy, adjuvant nivolumab was recently found to increase disease-free survival.[31]

The nonradical resection rate was significantly higher among patients with recurrences at the anastomosis or gastric conduit. Although a transthoracic esophagectomy results in more R0 resections and higher lymph node yield,[15] it did not result in lower recurrence rates. In fact, multivariable logistic regression showed

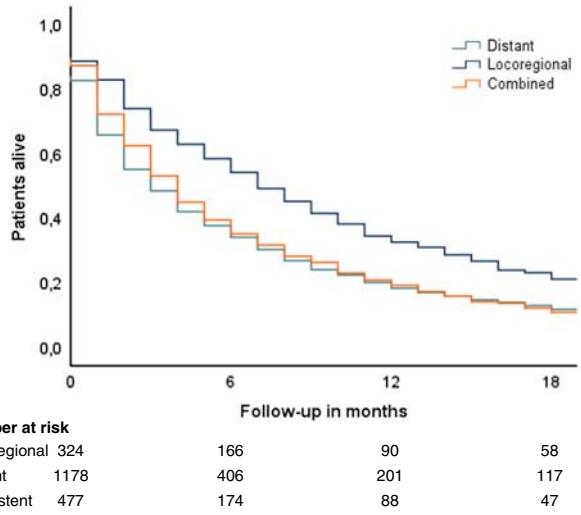
TABLE 2. Univariable and Multivariable Analysis of Factors Associated With Recurrent Esophageal Cancer After Esophagectomy With Curative Intent

	Univariable		Multivariable	
Associated Factors	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age				
> 65 y	Ref		Ref	
≤ 65 y	1.27 (1.13–1.43)	< 0.001	1.27 (1.12–1.45)	< 0.001
Sex				
Female	Ref		Ref	
Male	1.32 (1.14–1.53)	< 0.001	1.23 (1.04–1.46)	0.015
Tumor location				
Distal	Ref			
GEJ	1.08 (0.95–1.24)	0.242		
Tumor histology				
Adenocarcinoma	Ref		Ref	
Squamous cell carcinoma	0.61 (0.51–0.73)	< 0.001	0.73 (0.59–0.89)	0.001
cT-stage				
T1	Ref		Ref	
T2	2.54 (1.78–3.61)	< 0.001	2.02 (1.39–2.93)	< 0.001
T3	4.38 (3.15–6.09)	< 0.001	2.71 (1.90–3.85)	< 0.001
T4	5.29 (3.28–8.52)	< 0.001	3.03 (1.81–5.08)	< 0.001
cN stage				
N0	Ref			
N+	1.13 (1.10–1.17)	< 0.001		
Neoadjuvant treatment				
No	Ref			
Yes	1.15 (0.98–1.35)	0.097		
Surgical approach				
Minimally invasive	Ref		Ref	
Hybrid	0.75 (0.49–1.14)	0.177	0.67 (0.43–1.06)	0.085
Open	1.18 (1.05–1.33)	0.006	1.15 (1.00–1.33)	0.049
Esophageal resection				
Transthoracic	Ref		Ref	
Transhiatal	0.92 (0.82–1.04)	0.175	0.83 (0.72–0.96)	0.013
Radicality				
R0	Ref		Ref	
R+	2.69 (2.06–3.52)	< 0.001	1.36 (1.02–1.83)	0.040
Response to neoadjuvant treatment				
No	3.64 (2.76–4.80)	< 0.001		
Partial	2.41 (2.03–2.86)	< 0.001		
Complete	Ref			
(y)pT-stage				
T0	Ref		Ref	
T1	1.18 (0.96–1.45)	0.114	1.11 (0.89–1.39)	0.348
T2	1.97 (1.62–2.39)	< 0.001	1.49 (1.21–1.83)	< 0.001
T3	3.71 (3.14–4.40)	< 0.001	2.07 (1.71–2.51)	< 0.001
T4	6.75 (3.32–13.71)	< 0.001	2.88 (1.32–6.30)	0.008
(y)pN stage				
N0	Ref		Ref	
N+	1.36 (1.32–1.40)	< 0.001	1.25 (1.21–1.30)	< 0.001
Lymph node harvest				
≤ 15	1.04 (0.93–1.17)	0.477		
> 15	Ref			

cN indicates clinical N stage; cT, clinical T-stage; pN, pathological N stage; pT, pathological T-stage.

transthoracic esophagectomy associated with recurrence, while recurrence rates after transthoracic and transhiatal esophagectomy were comparable (in line with previous studies).[12,14] This finding might be explained by confounding by indication. According to the IVORY study, patient selection for both procedures differed, as patients selected for transthoracic procedures were younger, and had higher pathological T and N stages,[15] which are all associated with a higher risk of recurrence. The ongoing CARDIA trail will elucidate the preferred procedure for gastroesophageal junction tumors.[32] Compared with transhiatal extended gastrectomy, transthoracic esophagectomy is hypothesized to result in more R0 resections with subsequent lower recurrence rates.

Multivariable analysis found patients aged ≤ 65 years faced a greater risk of recurrent disease, which is consistent with the literature.[33] This observation may be a result of more advanced tumor characteristics in younger patients, as they are more frequently diagnosed with higher tumor stages, positive regional lymph nodes and distant metastasis.[34,35] The authors hypothesize that the association of open surgery and disease recurrence might, at least partially, be explained by the simultaneous implementation of

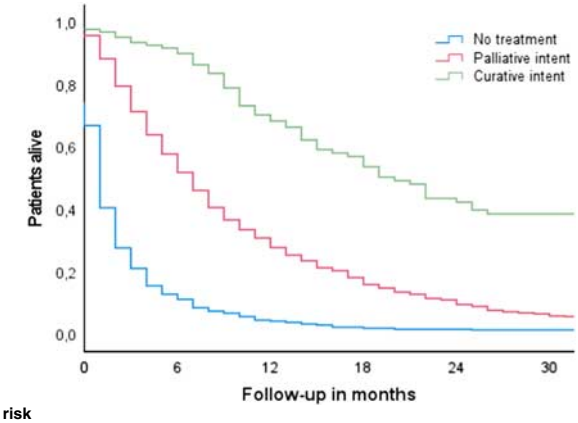


Number at risk				
Locoregional	324	166	90	58
Distant	1178	406	201	117
Coexistent	477	174	88	47

FIGURE 1. Site-specific survival of patients with recurrent esophageal cancer after esophagectomy (locoregional vs. distant: HR: 0.74, 95% CI: 0.65–0.84, $P < 0.001$).

minimally invasive surgery and neoadjuvant chemoradiotherapy in the Netherlands,[15] of which the latter results in fewer locoregional recurrences.[25,28,29] Also, open surgery may cause greater surgical trauma associated with a more profound depressed immune response.[36] In addition, the more extended lymphadenectomy during minimally invasive esophagectomy might reduce the possibility of residual malignant tissue.

There is a considerable discordance between clinical and pathological TNM staging of esophageal cancer.[37] For T-stage, both clinical and pathological stage were increasingly associated with disease recurrence, which is in line with literature.[22,38] However, while positive pathological N stage was found to be associated with disease recurrence in multivariable analysis, clinical N stage was not. The ongoing TIGER study will provide more insight in the distribution of esophageal lymph node metastases and the extent of lymphadenectomy.[39]



No. at risk						
No treatment	725	85	27	13	9	6
Palliative intent	910	480	242	130	74	38
Curative intent	123	104	72	52	36	28

FIGURE 2. Postrecurrence survival stratified by intent of recurrence treatment (curative intent vs. no treatment: HR: 0.23, 95% CI: 0.18–0.29, $P < 0.001$; palliative intent vs. no treatment: HR: 0.37, 95% CI: 0.33–0.41, $P < 0.001$).

Patients with solely locoregional esophageal cancer recurrences had better survival than those with distant recurrences. This improved survival is consistent with the findings of previous studies,[9,10,23] and could partly be explained by the more frequent option of (curatively intended) recurrence treatment for locoregional lesions.

In the case of esophageal cancer recurrence, several factors influence the intent and type of treatment, such as performance status, prior treatment, site of recurrence, and patient preferences, although evidence-based guidelines for recurrence treatment are lacking. In the current study, time to recurrence differed significantly between treatment intents, as patients with early recurrences (ie, in the first postoperative year) more often received palliative treatment. A median postrecurrence survival of 20 months was observed after curatively intended recurrence treatment, which contrasts sharply with the 1-month median survival when no tumor targeting treatment was administered (ie, best supportive care).

This nationwide cohort study provides important prognostic information for clinicians involved in the treatment of (recurrent) esophageal cancer, which can aid in the surveillance and counseling of esophageal cancer patients based on "daily clinical practice," with results generalizable to the overall population. Whether or not active postoperative surveillance is beneficial for patients at higher risk of recurrence or patients with solely locoregional recurrence who might benefit from timely diagnosis and treatment is to be investigated in prospective studies.

Some limitations need to be considered when interpreting the results of this study. First, due to the multicenter, retrospective nature of this study, intercenter variation in initial treatment of esophageal cancer and management of recurrent esophageal cancer may be present. However, it should be noted that with the introduction of the Dutch Upper-GI Cancer Audit in 2011, intercenter variation was likely reduced. Second, symptom-based follow-up could induce a selection bias in which the threshold for additional diagnostics differs per patient, potentially resulting in delayed diagnosis in older or frail patients. Third, quality of life—an important outcome measure regarding recurrent (esophageal) cancer—and exact recurrence treatment specifications were not available. Fourth, this study was a post hoc analysis of the IVORY study,[15] with data available from 18 out of 23 Dutch centers providing surgical esophageal cancer care for the period 2007–2010, and all 23 centers from 2011 onwards. Lastly, for patients registered with multiple recurrence sites, the site of first recurrence was unknown, which could be due to both the extent of recurrence at diagnosis and nondistinctive data registration. It was also not possible to discriminate patients with oligorecurrence.

In conclusion, this study confirms the aggressive nature of esophageal cancer with high recurrence rates after curative treatment for distal esophageal and gastroesophageal junction cancer. The risk of recurrence was higher in patients with a higher tumor stage, nonradical resection, and positive lymph node harvest, among other factors. Overall, patients with recurrent disease had limited survival prospects, although median postrecurrence survival of patients treated with curative intent reached 20 months. By reporting the patterns, predictors and survival of esophageal cancer recurrence, important prognostic information is provided that can aid in the surveillance and counseling of esophageal cancer patients who undergo potentially curative esophagectomy.

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DISCUSSANTS

Christiane Bruns (Cologne, Germany)

This study was a post-hoc analysis of the nationwide IVORY study, which is a retrospective cohort study evaluating the trends in care and postoperative outcomes for patients with distal esophageal and gastroesophageal junction cancer of 23 hospitals in the Netherlands, in 2007-2016 (follow-up until January 2020).

They were able to recognize 4,626 patients, of which 45.1% developed recurrent disease at a median of 11 months postoperatively. Most of them had distant metastases (59.8%). Disease recurrences were most frequently hepatic (26.2%), or pulmonary (25.1%). Young age ($\leq$65 y), male sex, adenocarcinoma, open surgery, transthoracic esophagectomy, non-radical

resection, higher T-stage, and tumor positive lymph nodes were significantly associated with disease recurrence. Overall, median post-recurrence survival was 4 months. After curatively intended treatment for recurrence, median survival was 20 months. Survival after locoregional recurrence was favorable compared to distant recurrence.

The increasing focus on the management of recurrent disease is a relevant topic after esophageal cancer surgery, with an expanding armamentarium of treatment options now available, including, for example, immunotherapy and local ablative techniques. While the reporting of prognostic factors for esophagogastric cancer is not particularly novel, the reporting of recurrence patterns and intervals to recurrence, particularly in this cohort treated mostly with CROSS and MIE, is of interest for the community. In any case, there are still some aspects of discussion:

First, the authors found out that even complete responders after CRTx or CTx had disease recurrence. It would be interesting to know what kind of disease recurrence (local vs. distant) this was, and following this, at what time the disease recurrence occurred?

Second, in AC and SCC, the most frequent locoregional recurrence was observed at the anastomosis and gastric conduit, although most patients received a R0 resection ("R0 resections were defined as no gross or microscopic tumor remains in the luminal and circumferential resection margins"). Could you explain this in more detail?

Third, the authors finally concluded that this study confirmed the aggressive nature of esophageal cancer with high recurrence rates after curative treatment for distal esophageal and gastroesophageal junction cancer. By reporting the patterns, the predictors and survival of esophageal cancer recurrence, important prognostic information is provided that can aid in the surveillance and counseling of esophageal cancer patients, who undergo potentially curative esophagectomy.

Finally, what would you change in your clinical routine based on the described pattern and predictors of recurrence, with respect to diagnostic tools during follow-up after surgery, the alteration of standards in neoadjuvant treatment protocols for locally advanced esophageal cancer, patient selection, and surgical procedures?

Response from Sofie Henckens (Amsterdam, The Netherlands)

Thank you very much for your useful questions. Indeed, the recurrence rate did significantly differ between the various responses to the neoadjuvant therapy groups. We saw that, of those patients with no response to neoadjuvant therapy, 60% had recurrent disease, while it was 50% for partial responders, and only 30% for patients with a complete response. If we look at the distribution pattern of recurrences, we did not see these clear differences. We did see that after a complete response, the proportion of locoregional disease was a bit lower, but not significantly. With a complete response, it took a median of 11 months for recurrent disease to develop. Which was 10 months after partial response and 8 months without tumor regression after neoadjuvant treatment.

In the entire group, the R0 resection rate was 94%. However, the patients that developed recurrence at the anastomosis had a non-radical resection rate twice as high as the overall population. In the overall population, it was 7% versus 15% for these patients that developed recurrence at the anastomosis. I think that this underlines the importance of striving for complete resections. But also, other patients with R0 resection, developed locoregional recurrence at the anastomosis, which, I expect, was due to either lymph node metastases involving the esophageal/gastric wall, or maybe spillage of tumor cells.

Your third question is very relevant. Regarding diagnostic tools, we did identify some patients that reached long-term follow-up, and they were most often patients with locoregional disease and curatively treated. However, this group of patients was too small to reliably analyze factors which could identify these patients in an early stage, as they could probably benefit most from follow up with routine imaging, instead of a clinical follow up. Therefore, based on these data, I wouldn't directly change our current follow-up strategy and make low-threshold CT scans.

Regarding neoadjuvant therapy, we did see a lower recurrence rate and lower proportion of locoregional disease after chemoradiotherapy than after chemotherapy only. This might lead us to believe that chemoradiotherapy leads to better locoregional tumor control. However, again, based on these data, I don't think it's possible to give a preference because you also need to consider the morbidity of neoadjuvant treatment strategies. Most importantly, I think that we are not aware of what the exact indications have been for the given neoadjuvant therapy. Neoadjuvant chemotherapy may have been chosen for cancers with more gastric involvement, or in patients, for whom the radiation field would have been too extensive, causing selection bias. Therefore, it is not possible to draw solid conclusions concerning the preferred neo-adjuvant regimen solely on the results of this study. In future research, it would be highly interesting to further develop better systemic therapy, such as the recent implementation of adjuvant nivolumab.

Lastly, regarding patient selection and surgical procedures, a younger age, male gender, open surgery, pN+ and R+, adenocarcinoma, and transthoracic esophagectomy were all associated with a higher risk of recurrence. The patient factors cannot be modified, but the treatment factors can. Regarding open surgery, in the Netherlands, over 98% of esophagectomies are currently performed by the minimally invasive approach, and increasingly, by the transthoracic approach, leading to more R0 resections. Additionally, we think that it is necessary to further standardize surgical procedures, and to improve the quality of lymphadenectomy.

Michael Kerin (Galway, Ireland)

I'm intrigued by this data overall. At the average surgical oncology meeting, where we talk about chemotherapy or radiotherapy use, I think that these data give us the opportunity to address issues around centralization in surgery, and high- versus low-volume units across the Netherlands.

Presumably, there was a structured approach in place, so that every unit would have the same indications and type of interventions. I wonder whether you had analyzed the data from the point of view of the high-volume versus low-volume units, or high-volume versus low-volume surgeons. Do you have any views on the quality of surgery, in terms of determining the long-term outcomes for the esophageal cancer population?

Response from Sofie Henckens (Amsterdam, The Netherlands)

We have not done this yet. If we would like to do so, we would need to discuss this with all the involved authors first.

Arnulf H. Hölscher (Essen, Germany)

Was there a correlation with tumor markers concerning the different subgroups?

Response from Sofie Henckens (Amsterdam, The Netherlands)

We have not looked at this because, in the Netherlands, there are currently no tumor markers that are used in the treatment for esophageal cancer. This is interesting for future research.