A population-based study in resected esophageal or gastroesophageal junction cancer aligned with CheckMate 577

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Abstract

Background: Results of CheckMate 577 show an improved disease-free survival for patients with resected esophageal or gastroesophageal junction cancer treated with adjuvant nivolumab compared with placebo (22.4 *versus* 11.0 months). Population-based data can provide insights in outcomes from clinical practice. The aim of our study was to investigate disease-free and overall survival in a nationwide population aligned with the inclusion criteria of CheckMate 577.

Patients and Methods: Resected patients with stage II/III esophageal or gastroesophageal junction cancer (2015–2016) treated with neoadjuvant chemoradiotherapy were selected from the Netherlands Cancer Registry. Patients with cervical esophageal cancer, irradical resection, or complete pathological response were excluded. Disease-free and overall survival were assessed from 12 weeks after resection using Kaplan-Meier methods. In addition, to adjust for differences in characteristics between CheckMate 577 and our population-based cohort, a matching-adjusted indirect comparison was performed for pathological lymph node status and pathological tumor status.

Results: We identified 634 patients. Sixty percent of patients were diagnosed with recurrence or were deceased at the end of follow-up. Median disease-free survival was 19.7 months and median overall survival was 32.2 months. After the matching procedure, the median disease-free survival was 17.2 months and median overall survival was 28.2 months.

Conclusions: Disease-free survival in our population-based study was considerably longer than the placebo population of CheckMate-577 (19.7 *versus* 11.0 months). Possible explanations are differences in characteristics, quality of esophageal cancer care, or differential strategies for evaluation of recurrence. In the Netherlands postoperative imaging is not part of the standard follow-up as opposed to the standard postoperative imaging in the CheckMate 577 trial. The difference in postoperative imaging could partially explain the longer disease-free survival observed in our study. Quality and optimization of current treatment modalities remain important aspects of esophageal cancer care.

Keywords: disease-free survival, esophageal cancer, gastroesophageal junction cancer, population-based

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Introduction

Neoadjuvant chemoradiotherapy followed by surgery is a standard of care for patients with resectable locally advanced esophageal cancer.[1,2] Outcomes are, however, still poor, with median disease-free survival of 2.5 years and overall survival of 4 years.[1,3] Currently, adjuvant treatment is not part of the standard of care for esophageal cancer due to unconvincing results of clinical studies.[4–6] The addition of adjuvant treatment

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could particularly be interesting for patients with residual pathological disease after neoadjuvant chemoradiotherapy who have poorer outcomes compared with patients without residual pathological disease.[7–9]

Recently, the phase 3 CheckMate 577 trial showed positive outcomes after adjuvant treatment.[10] In CheckMate 577, patients with stage II/III esophageal or gastroesophageal junction cancer who received neoadjuvant chemoradiotherapy followed by radical resection and who had residual pathological disease were randomized for adjuvant nivolumab or placebo (NCT02743494). The disease-free survival of patients who received adjuvant nivolumab improved to a median of 22.4 months compared with 11.0 months in patients who received adjuvant placebo.[10] Mature data on overall survival have not been reported yet.

Although randomized controlled trials are the gold standard for the introduction of new treatment strategies, population-based data can complement randomized controlled trials by providing information regarding outcomes in clinical practice. Population-based studies better reflect the clinical practice by including frail and elderly patients, and patients with comorbidities. Based on the inclusion of these patients, we hypothesize that disease-free and distant metastasis-free survival in a population-based study will be shorter compared with CheckMate 577. In this study, we selected patients from the nationwide Netherlands Cancer Registry (NCR) who complied with the most important inclusion criteria of CheckMate 577, and subsequently investigated the characteristics and outcomes of this population.

Methods

Study population

Patients diagnosed with stage IIA-B or IIIA-C adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction/cardia in 2015–2016 according to the seventh edition of the TNM Classification of Malignant Tumors who had received neoadjuvant chemoradiotherapy followed by surgery were selected from the NCR.[11] The NCR is a population-based cancer registry that covers the total Dutch population and is based on notification of all newly diagnosed malignancies by the national automated pathology archive. Specially trained data managers of the NCR routinely extract information on diagnosis, tumor stage, and treatment from medical records. Dutch guidelines recommend follow-up after surgery at 3 weeks, 6 weeks (optional), every 3 months in the first year, every 6 months in the second year, and thereafter yearly up to 5 years, with imaging only after patients experience symptoms.[12] Data on disease recurrence were collected in the second half of 2019. Information on vital status was available through linkage of the NCR with the Dutch Personal Records Database and was updated until February 1, 2020. According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. Based on current Dutch legislation, it is not necessary to retrieve informed consent from patients for registration into the NCR. The privacy review board of the NCR reviews all data requests for studies with data of the NCR regarding privacy issues and approved this study. This study was also approved by the scientific committee of the Dutch Upper GI Cancer Group.

In total, 1096 patients with stage II/III disease who received neoadjuvant chemoradiotherapy followed by surgery were available for inclusion (Figure 1). Patients from two hospitals were excluded ($n = 73$), as from these hospitals data on follow-up were unavailable due to logistic reasons. One patient was excluded due to receiving chemotherapy prior to neoadjuvant chemoradiotherapy. Patients receiving trastuzumab and pertuzumab in combination with neoadjuvant chemoradiotherapy as part of the TRAP trial were excluded ($n = 27$).[13] Adjuvant chemotherapy is not standard of care for esophageal cancer in the Netherlands and patients who received adjuvant S1 and oxaliplatin according to the SOX trial or who received adjuvant nivolumab according to CheckMate 577 were excluded ($n = 22$).[6,10] To align our population with CheckMate 577, patients with cervical esophageal cancer ($n = 0$), irradical resection (R1/R2) or unknown radicality ($n = 66$), and without residual pathological disease (ypT0N0) ($n = 212$) were excluded. To account for time from resection until randomization of 4 to 16 weeks in CheckMate 577, patients who were deceased within 12 weeks after resection ($n = 44$) or patients who had recurrence within 12 weeks after resection ($n = 17$) were excluded.

Treatment definitions

Neoadjuvant chemoradiotherapy was defined as chemotherapy prior to surgery with concurrent radiotherapy with an overlap of at least 7 days and

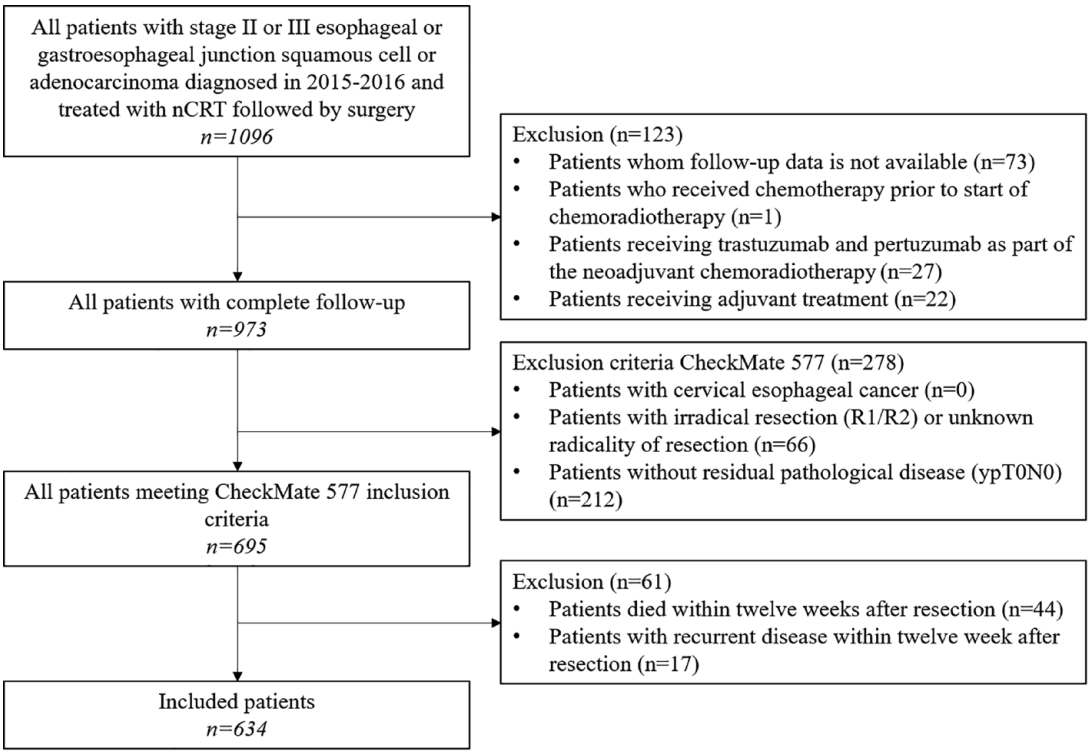


Figure 1. Flowchart of patient selection.
nCRT, neoadjuvant chemoradiotherapy.

maximum dose per fraction of 1.8 gray (Gy).[2] Total radiation dose was classified as <41.4, 41.4, or >41.4 Gy. Chemotherapy was classified as carboplatin with paclitaxel or docetaxel. Surgical resection was defined as esophagectomy (transhiatal or transthoracic) or total gastrectomy.

Disease-free survival, distant metastasis-free survival, and overall survival

Disease-free, distant metastasis-free, and overall survival were assessed from 12 weeks after date of resection to mimic randomization of 4 to 16 weeks after resection.[10] Disease-free survival was assessed until date of disease recurrence or death, whichever occurred first, or until the end of follow-up. Distant metastasis-free survival was assessed until the date of the first distant metastasis or death, whichever occurred first, or until the end of follow-up. All deaths without prior recurrence were included as a recurrence event. Patients still alive and without recurrence were censored at the date of last hospital visit. Overall survival was assessed until death or end of follow-up for vital status. Postrecurrence survival was assessed from date of disease recurrence until death or end of follow-up for vital status.

Matching-adjusted indirect comparison

To adjust for differences in characteristics between CheckMate 577 and our population, a matching-adjusted indirect comparison (MAIC) was performed as previously described.[14] The MAIC was performed for pathological lymph node status and pathological tumor status. These characteristics were selected based on availability, magnitude of difference in distribution between the CheckMate 577 placebo population and our population, and magnitude of difference in disease-free survival of subgroups in CheckMate 577.[10] In short, 1000 random samples with a sample size of 80% of the population in our study that mimicked the distribution of pathological lymph node and pathological tumor status of CheckMate 577 were retrieved. The mean of the median survival with 95% confidence interval (CI) for each of the 1000 subsets was calculated.

Statistical analyses

Patient and tumor characteristics were compared with chi-square test, Fisher's exact test, or Student's *t* test where appropriate. To evaluate disease-free, distant metastasis-free, and overall survival, Kaplan-Meier methods were used.

Univariable and multivariable Cox regression hazard analyses were conducted to assess association of patient and tumor characteristics with disease-free and overall survival. Variables were selected based on CheckMate 577 and availability in the NCR. Tumor-cell PD-L1 expression and HER2 status at primary diagnosis were not available in the NCR due to current irrelevance in clinical practice. To avoid multicollinearity, tumor regression of the primary tumor and pathological tumor status could not both be included and tumor regression was included instead of the pathological tumor status due to small numbers in distribution of the pathological tumor status. To test the proportional hazard assumptions, time-dependent covariates were created as a function of the survival time. The p values < 0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

The study population consisted of 634 patients (Figure 1). The proportion of patients with clinical disease stage II or III was 43% and 57%, respectively (Table 1). Six percent of patients had complete regression of the primary tumor, 26% subtotal regression, 58% partial regression, 6% no regression, and 4% was unknown. The ypN stage was N+ in 50% of patients. The distribution in the characteristics of the postmatched population is presented in Supplementary Table 1.

In total, 383 events of disease recurrence ($n = 328$) or death ($n = 55$) were observed. Among patients with disease recurrence, in 81% of patients the diagnosis was established after patients experienced symptoms, in 18% through a follow-up visit, and in 1% diagnosis was coincidental. Locoregional recurrence was diagnosed in 27 of 634 patients (4%), distant recurrence in 120 of 634 patients (19%), and combined locoregional and distant recurrence in 181 of 634 patients (29%). In patients with distant or combined locoregional and distant recurrence, the most common distant locations were distant lymph nodes (40%), liver (29%), lung (29%), and peritoneal (27%).

A total of 196 of 634 patients (31%) received subsequent therapy, including surgery ($n = 11$), chemoradiotherapy ($n = 17$), systemic therapy ($n = 106$), and radiotherapy ($n = 62$). In patients receiving systemic therapy, 56 of 106 patients received capecitabine plus oxaliplatin (53%), 18 of 106 received carboplatin plus paclitaxel (17%), and 12 of 106 patients received a trastuzumab-containing regimen (11%).

Disease-free survival, distant metastasis-free survival, and overall survival

Median disease-free survival was 19.7 (95% CI = 16.5–22.8) months, median distant metastasis-free survival was 21.4 (95% CI = 17.9–24.9) months, and median overall survival was 32.2 (95% CI = 26.7–36.2) months (Figure 2). In patients with disease recurrence, the postrecurrence survival was 4.4 (95% CI = 3.7–6.2) months. After the matching procedure, median disease-free survival was 17.2 (95% CI = 16.2–18.4) months, median distant metastasis-free survival was 18.5 (95% CI = 17.6–20.1) months, and median overall survival was 28.2 (95% CI = 25.9–29.5) months.

Clinical disease stage III at diagnosis [$p < 0.001$; hazard ratio (HR) = 1.47, 95% CI = 1.20–1.81; reference category clinical disease stage II), subtotal regression of the primary tumor ($p = 0.004$; HR = 0.69, 95% CI = 0.54–0.89; reference category partial regression), pathological lymph node stage ypN+ ($p < 0.001$; HR = 2.07, 95% CI = 1.68–2.54; reference category stage ypN0), and poorly/undifferentiated tumors ($p = 0.003$; HR = 1.40, 95% CI = 1.13–1.75; reference category well/moderate differentiated tumors) were univariably associated with disease-free survival (Figure 3; Table 2).

Multivariable analyses showed independent association of complete regression of the primary tumor (ypT0N+) with a better disease-free and overall survival and showed independent association of pathological lymph node stage ypN+, clinical disease stage III, and poorly/undifferentiated tumors with a poorer disease-free and overall survival.

Discussion

This study shows that in a population-based cohort, patients with resected stage II/III esophageal or gastroesophageal junction cancer and residual pathological disease after neoadjuvant chemoradiotherapy had a median disease-free survival of 19.7 months, median distant metastasis-free survival of 21.4 months, and median

Table 1. Characteristics of patients at primary diagnosis.

Characteristic	All patients	Recurrence or deceased	No recurrence	*p*[a]
Total, *n* (%)	634 (100.0)	383 (60.4)	251 (36.6)	
Male	515 (81.2)	316 (82.5)	199 (79.3)	0.31
Age in years, median (IQR)	65(59–70)	66(59–70)	65(59–70)	0.58
Comorbidities, *n* (%)				0.15
0	338 (53.3)	194 (50.7)	144 (57.4)	
1	199 (31.4)	131 (34.2)	68 (27.1)	
⩾2	78 (12.3)	49 (12.8)	29 (11.6)	
Unknown	19 (3.0)	9 (2.3)	10 (4.0)	
ASA score prior to surgery, *n* (%)				0.39
Class I	92 (14.5)	50 (13.1)	42 (16.7)	
Class II	391 (61.7)	234 (61.1)	157 (62.5)	
Class III	116 (18.3)	78 (20.4)	38 (15.1)	
Class IV	4 (0.6)	2 (0.5)	2 (0.8)	
Unknown	31 (4.9)	19 (5)	12 (4.8)	
Tumor location, *n* (%)				0.28
Proximal third esophageal	2 (0.3)	1 (0.3)	1 (0.4)	
Middle third esophageal	61 (9.6)	42 (11)	19 (7.6)	
Distal third esophageal	523 (82.5)	316 (82.5)	207 (82.5)	
Overlapping/Unknown esophageal	12 (1.9)	5 (1.3)	7 (2.8)	
Gastroesophageal junction – Cardia	36 (5.7)	19 (5)	17 (6.8)	
Clinical disease stage at diagnosis, *n* (%)				0.002
II	270 (42.6)	144 (37.6)	126 (50.2)	
III	364 (57.4)	239 (62.4)	125 (49.8)	
Tumor regression of primary tumor, *n* (%)				0.02
Complete	39 (6.2)	23 (6.0)	16 (6.4)	
Subtotal	164 (25.9)	82 (21.4)	82 (32.7)	
Partial	368 (58.0)	236 (61.6)	132 (52.6)	
None	35 (5.5)	25 (6.5)	10 (4)	
Unknown	28 (4.4)	17 (4.4)	11 (4.4)	
Pathological tumor status, *n* (%)				<0.001
ypT0	39 (6.2)	23 (6.0)	16 (6.4)	
ypT1	132 (20.8)	62 (16.2)	70 (27.9)	

(Continued)

Table 1. (Continued)

Characteristic	All patients	Recurrence or deceased	No recurrence	p^a
ypT2	176 (27.8)	96 (25.1)	80 (31.9)	
ypT3	285 (45)	201 (52.5)	84 (33.5)	
ypT4	2 (0.3)	1 (0.3)	1 (0.4)	
Pathological lymph node status, *n* (%)				<0.001
ypN0	317 (50.0)	151 (39.4)	166 (66.1)	
ypN+	317 (50.0)	232 (60.6)	85 (33.9)	
Histology, *n* (%)				0.89
Adenocarcinoma	527 (83.1)	319 (83.3)	208 (82.9)	
Squamous cell carcinoma	107 (16.9)	64 (16.7)	43 (17.1)	
Lauren classification, *n* (%)				0.95
Intestinal	370 (58.4)	223 (58.2)	147 (58.6)	
Diffuse	65 (10.3)	41 (10.7)	24 (9.6)	
Mixed	7 (1.1)	4 (1.0)	3 (1.2)	
Indeterminate	30 (4.7)	20 (5.2)	10 (4)	
Adenocarcinoma NOS	55 (8.7)	31 (8.1)	24 (9.6)	
Not applicable	107 (16.9)	64 (16.7)	43 (17.1)	
Tumor differentiation, *n* (%)				0.04
Well/moderate	326 (51.4)	181 (47.3)	145 (57.8)	
Poorly/undifferentiated	221 (34.9)	145 (37.9)	76 (30.3)	
Unknown	87 (13.7)	57 (14.9)	30 (12)	
Type of resection, *n* (%)				
Transhiatal esophagectomy	95 (15.0)	60 (15.7)	35 (13.9)	0.48
Transthoracic esophagectomy	533 (84.1)	318 (83.0)	215 (85.7)	
Ivor Lewis	187 (35.1)	68 (31.6)	119 (37.4)	
McKeown	332 (62.3)	142 (66)	190 (59.7)	
Unknown	14 (2.6)	5 (2.3)	9 (2.8)	
Total gastrectomy	6 (0.9)	5 (1.3)	1 (0.4)	
Total radiation dose, *n* (%)				0.48
<41.4 Gy	1 (0.2)	1 (0.3)	0 (0.0)	
41.4 Gy	612 (96.5)	367 (95.8)	245 (97.6)	
>41.4 Gy	21 (3.3)	15 (3.9)	6 (2.4)	

(Continued)

Table 1. (Continued)

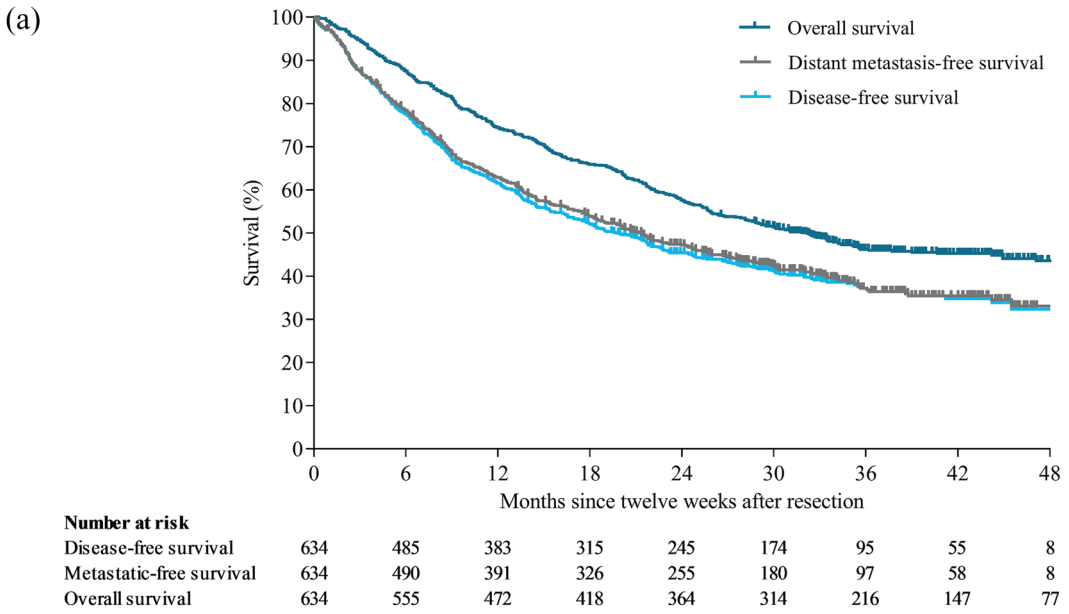
Characteristic	All patients	Recurrence or deceased	No recurrence	*p*[a]
Type of neoadjuvant chemotherapy, *n* (%)				0.52
Carboplatin and paclitaxel	632 (99.7)	381 (99.5)	251 (100)	
Carboplatin and docetaxel	2 (0.3)	2 (0.5)	0 (0.0)	
Number of neoadjuvant chemotherapy cycles, *n* (%)				0.11
⩽ 4	64 (10.1)	46 (12)	18 (7.2)	
5	556 (87.7)	330 (86.2)	226 (90)	
⩾6	14 (2.2)	7 (1.8)	7 (2.8)	

ASA, American Society of Anesthesiology; Gy, gray; IQR, interquartile range; NOS, not otherwise specified.
[a]*p* values reflect chi-square statistics or Fisher's exact test for categorical variables and Student's *t* test for age.

overall survival of 32.2 months. The reported disease-free survival and distant metastasis-free survival are longer than the median disease-free survival (11.0 months) and distant metastasis-free survival (17.6 months) of the placebo population in CheckMate 577, while overall survival results of CheckMate 577 are not yet available.

Our results are surprising as often overall outcomes of population-based studies do not outcompete clinical trial results due to strict inclusion and exclusion criteria of clinical trials. In population-based studies, survival outcomes have been shown to be similar or less compared with clinical trials.[15–17] The difference in outcomes between CheckMate 577 and our population could result from the level of quality of esophageal cancer care provided. Since the Dutch CROSS trial, neoadjuvant chemoradiotherapy with carboplatin plus paclitaxel has become part of the standard of care for patients with locally advanced esophageal cancer in the Netherlands.[2] In our population 97% of patients received 41.4 Gy and 99.7% received carboplatin plus paclitaxel compared with 63% of patients receiving 41.4–50.4 Gy and 68% receiving carboplatin plus paclitaxel in the placebo arm of CheckMate 577. In the Netherlands, improvement in quality of surgery and reduction in complications after surgery were observed after centralization of esophageal surgery and the installment of the obligatory national surgical audit, the Dutch Upper GI Cancer Audit (DUCA).[18–21] The introduction of neoadjuvant chemoradiotherapy, centralization of surgery, and installment of the DUCA improved outcomes of patients with esophageal cancer in the Netherlands.[22] In CheckMate 577, investigators from 170 study locations in 29 countries worldwide participated, that is, an average of only one or two patients from the placebo population per center. Quality of esophageal cancer care could differ considerably between participating centers due to less experience with administering neoadjuvant chemoradiotherapy, lack of centralization of surgery, and absence of obligatory clinical audits, all affecting survival outcomes. In CheckMate 577, quality control of surgical resections was not performed. Furthermore, patients were only eligible for inclusion in CheckMate 577 if disease-free status was confirmed by a CT scan performed within 4 weeks prior to randomization. Although in our population patients with recurrence within 12 weeks after resection were excluded, this will not completely eliminate patients without a disease-free status according to the criteria of CheckMate 577. Of note, if these criteria would have been applied to our population even longer survival is expected.

An important difference between CheckMate 577 and our population is the evaluation of disease recurrence. In clinical practice in the Netherlands, imaging to detect recurrence is not routinely performed during follow-up care. The majority of patients in our population were diagnosed with recurrence after experiencing symptoms. Standard postoperative imaging in CheckMate 577 could partially explain the longer disease-free survival observed in our study. An earlier diagnosis, however, may not have a large effect on the



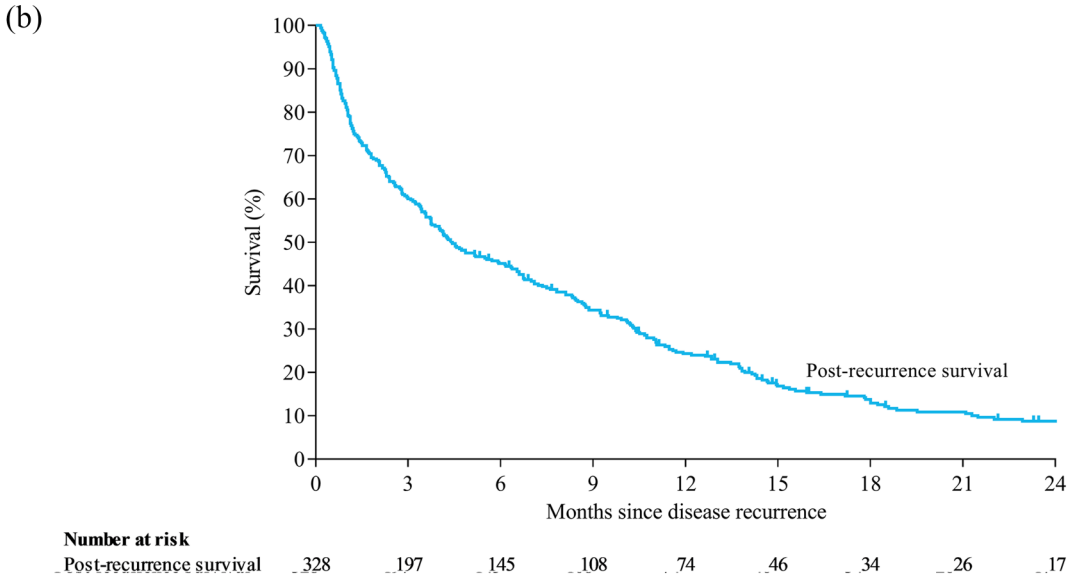


Figure 2. (a) Disease-free survival, distant metastasis-free survival and overall survival. (b) Postrecurrence survival.

prognosis, as treatment options after recurrence are limited and postrecurrence survival is poor.[23,24] To assess the true value of the addition of nivolumab in the adjuvant setting, overall survival data are eagerly awaited.

After the matching procedure for pathological lymph node and pathological tumor status, the postmatch population still had a longer disease-free and distant metastasis-free survival compared with the placebo population of CheckMate 577. Of note, after matching, the CheckMate placebo population was still younger (61 *versus* 65 years), had a slightly higher proportion of male patients (85% *versus* 82%), and had more patients with squamous cell carcinoma (29% *versus* 17%) compared with our postmatched population. None of these variables, however, were identified as factors associated with disease-free and overall survival in our population. The proportion of patients with gastroesophageal junction cancer was considerably lower in our population (6%) compared

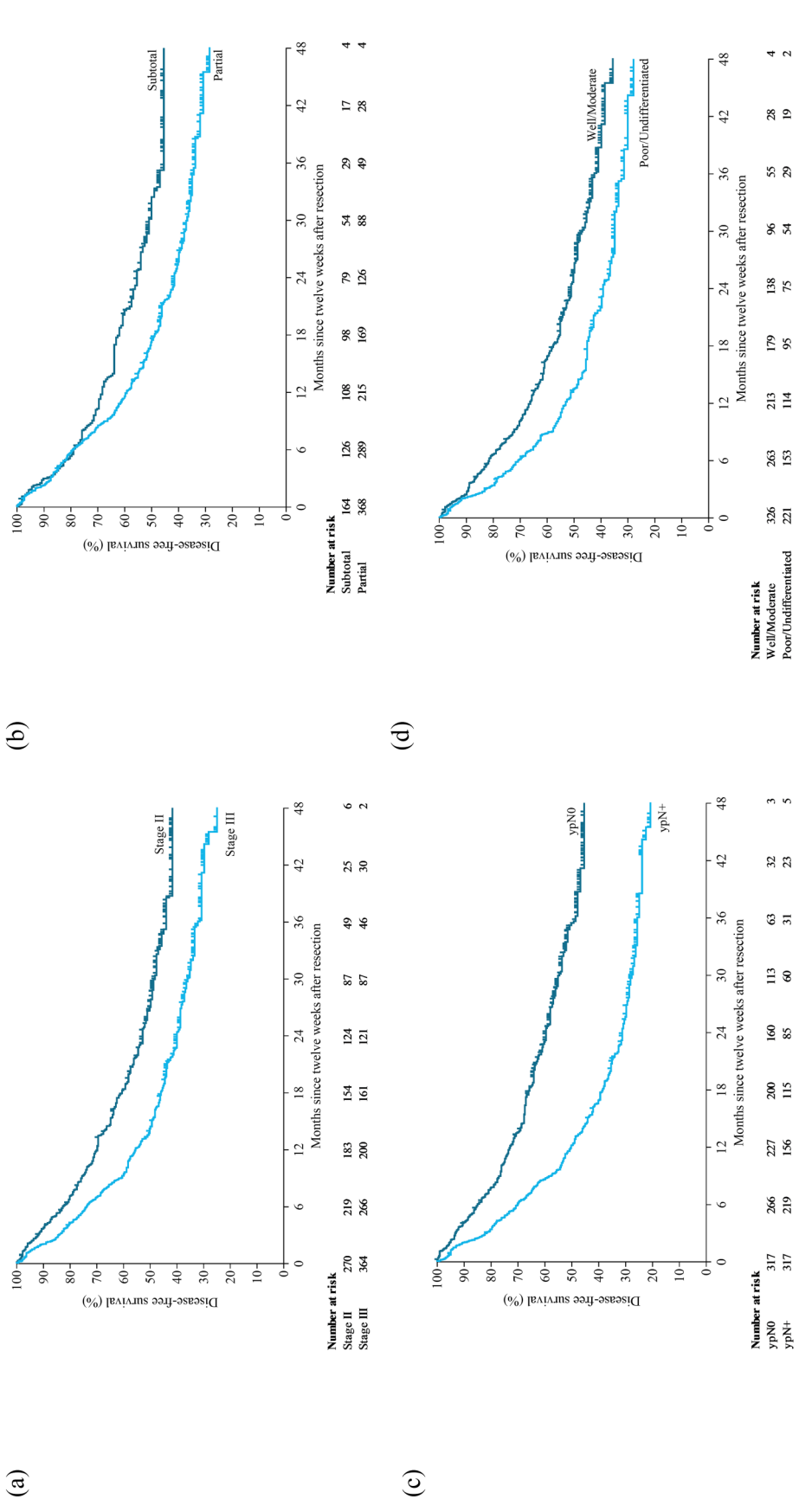


Figure 3. Disease-free survival stratified by (a) clinical disease stage at diagnosis, (b) tumor regression of the primary tumor, (c) pathological lymph node status and (d) tumor differentiation. Patients with complete, none or unknown tumor regression of the primary tumor (b), and patients with unknown tumor differentiation (d) were excluded due to limited sample size.

Table 2. Cox regression analyses for disease-free survival and overall survival.

Variable	Patients, *n*	Disease-free survival			Overall survival		
		Median DFS	Univariable regression, HR (95% CI)	Multivariable regression, HR (95% CI)	Median OS	Univariable regression, HR (95% CI)	Multivariable regression, HR (95% CI)
Sex							
Male	515	18.9	Reference		30.1	Reference	
Female	119	26.6	0.87 (0.67–1.13)	0.90 (0.68–1.20)	44.2	0.82 (0.62–1.08)	0.80 (0.59–1.08)
Age, years[a]	634	–	0.99 (0.99–1.01)	1.00 (0.99–1.02)	–	1.01 (1.00–1.02)	1.01 (1.00–1.03)
Comorbidities							
0	338	21.8	Reference		34.2	Reference	
1	199	16.4	1.21 (0.97–1.51)	1.26 (1.00–1.59)	25.9	1.24 (0.98–1.56)	1.28 (1.00–1.63)
⩾2	78	19.7	1.20 (0.88–1.64)	1.26 (0.90–1.77)	25.2	1.22 (0.88–1.69)	1.20 (0.84–1.72)
Unknown	19	36.1	0.74 (0.38–1.44)	0.95 (0.48–1.88)	37.7	0.72 (0.36–1.47)	0.97 (0.47–2.00)
ASA classification							
Class I	92	21.8	0.89 (0.65–1.21)	0.94 (0.68–1.30)	44.9	0.84 (0.61–1.16)	0.96 (0.69–1.35)
Class II	391	21.0	Reference		32.4	Reference	
Class III or IV	120	16.2	1.21 (0.94–1.56)	1.06 (0.80–1.39)	23.9	1.24 (0.95–1.61)	1.07 (0.80–1.43)
Unknown	31	20.6	1.03 (0.64–1.64)	0.96 (0.60–1.54)	27.5	1.05 (0.65–1.71)	1.03 (0.63–1.68)
Tumor regression of the primary tumor							
Complete	39	24.4	0.86 (0.56–1.32)	0.52 (0.33–0.82)	44.2	0.73 (0.46–1.17)	0.45 (0.28–0.74)
Subtotal	164	32.4	0.69 (0.54–0.89)	0.79 (0.61–1.02)	NR	0.70 (0.53–0.91)	0.80 (0.61–1.05)
Partial	368	17.2	Reference		26.2	Reference	
None	35	11.7	1.37 (0.91–2.07)	1.40 (0.91–2.14)	19.2	1.48 (0.97–2.25)	1.53 (0.99–2.36)
Unknown	28	21.4	0.85 (0.52–1.39)	0.74 (0.45–1.22)	NR	0.66 (0.38–1.16)	0.60 (0.34–1.06)
Pathological lymph node status					0		
ypN0	317	35.5			NR		
ypN +	317	12.2	2.07 (1.68–2.54)	2.08 (1.67–2.59)	21.7	2.02 (1.62–2.5)	2.12 (1.69–2.66)
Clinical disease stage at diagnosis							
II	270	27.0	Reference		48.5	Reference	
III	364	14.2	1.47 (1.20–1.81)	1.34 (1.08–1.67)	25.9	1.44 (1.16–1.79)	1.33 (1.06–1.66)
Histology							
Adenocarcinoma	527	19.6			32.2		
Squamous cell carcinoma	107	21.7	1.01 (0.77–1.32)	0.94 (0.65–1.35)	32.3	1.06 (0.81–1.40)	1.01 (0.69–1.47)

(Continued)

Table 2. (Continued)

Variable	Patients, *n*	Disease-free survival			Overall survival		
		Median DFS	Univariable regression, HR (95% CI)	Multivariable regression, HR (95% CI)	Median OS	Univariable regression, HR (95% CI)	Multivariable regression, HR (95% CI)
Tumor differentiation							
Well/moderate	326	25.7	Reference		44.9	Reference	
Poorly/ undifferentiated	221	13.5	1.40 (1.13–1.75)	1.41 (1.13–1.77)	21.7	1.59 (1.27–1.99)	1.63 (1.29–2.05)
Unknown	87	17.8	1.22 (0.91–1.65)	1.27 (0.93–1.72)	32.3	1.16 (0.84–1.60)	1.22 (0.87–1.70)
Tumor location							
Proximal third or middle third esophageal	63	16.5	1.16 (0.84–1.59)	1.35 (0.88–2.06)	26	1.27 (0.92–1.76)	1.51 (0.98–2.31)
Distal third esophageal	523	19.0	Reference			Reference	
Overlapping/ Unknown esophageal	12	34.8	0.54 (0.22–1.31)	0.58 (0.23–1.46)	NR	0.51 (0.19–1.37)	0.56 (0.20–1.54)
Gastroesophageal junction	36	32.0	0.74 (0.46–1.17)	0.67 (0.42–1.08)	48.5	0.86 (0.53–1.38)	0.79 (0.48–1.28)

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NR, not reached; OS, overall survival.
[a]Age is included as a continuous variable; therefore, the median disease-free and overall survival is not provided.

with the CheckMate 577 placebo population (41%). The limited proportion of patients with gastroesophageal junction cancer in our population compared with CheckMate 577 could be the result of discrepancies between classification of patients with Siewert type I tumors as lower (distal) esophageal instead of gastroesophageal junction.[25] In the CheckMate 577 placebo population, the disease-free survival was 20.6 and 8.3 months for patients with gastroesophageal junction and esophageal cancer, respectively.[10] Consequently, the disease-free survival of our population would expected to be longer if the proportion of patients with gastroesophageal junction cancer was higher.

Our study has several limitations. First, average time from surgical resection to randomization in CheckMate 577 was not mentioned in the publication. Patients, however, should have been randomized between 4 and 16 weeks after surgical resection. The majority of patients in the placebo population in CheckMate 577 (188 of 262 patients) were randomized ⩾10 weeks after surgical resection.[10] Based on this information, we decided to use an arbitrary cutoff of 12 weeks since resection to exclude patients who had recurrence or were deceased within 12 weeks since resection as these patients would probably be ineligible for adjuvant therapy. Subsequently, we calculated survival from 12 weeks since resection as otherwise we would have introduced immortal time bias as all patients survived at least 12 weeks since resection. Second, data for certain variables, for example, American Society of Anesthesiology (ASA) score prior to surgery and tumor regression of the primary tumor, were incomplete and might have resulted in suboptimal adjustment in the multivariable models. Third, postoperative imaging is not part of the standard follow-up in the Netherlands and postoperative imaging is only performed if a patient experiences symptoms. As a result, disease recurrence could have been detected at a later stage as compared with CheckMate 577, in which postoperative imaging was part of the standard follow-up and thus could explain the longer disease-free survival observed in our population. Finally, information on performance status was not available 12 weeks after resection and patients with Eastern Cooperative Oncology Group (ECOG) performance status of ⩾2 were not excluded. Inclusion of patients with a poorer

performance status, however, is not expected to have a positive effect on survival outcomes and could not explain the longer observed disease-free and distant metastasis-free survival.

The major strengths of our study are the nationwide population-based design to provide insights in the characteristics and outcomes of patients that would be eligible for adjuvant therapy in the clinical practice, and the high level of homogeneity in the administration of neoadjuvant chemoradiotherapy.

In conclusion, we showed that in our population-based study disease-free and distant metastasis-free survival were longer compared with the placebo population of CheckMate 577. This indicates that optimization of current strategies through centralization and clinical audits to ensure high-quality esophageal cancer care remain important aspects of esophageal cancer care and are as important as the development of novel treatment strategies. Administration of adjuvant therapy in patients with resected esophageal cancer or gastroesophageal junction cancer previously treated with neoadjuvant chemoradiotherapy should not be used to compensate for suboptimal treatment, but only be introduced if after good quality surgical care outcomes can be improved to an even higher level. We feel that patients should not be exposed to unnecessary treatment and toxicity as well as exposing society with the accompanying costs to compensate for poor surgical care. Overall survival results of CheckMate 577 will hopefully provide more insights on the true value of adjuvant nivolumab.

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Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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