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Induction chemotherapy followed by response evaluation and esophagectomy for advanced esophageal cancer

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ABSTRACT

Introduction: Patients with limited metastatic/advanced esophageal cancer not amenable for neoadjuvant therapy plus surgery have a poor prognosis and often receive palliative care. Alternatively, induction chemotherapy with response evaluation can be considered and in some patients surgery with curative intent may become feasible. The aim of this study was to evaluate the outcomes of patients treated with induction chemotherapy and to identify patient and/or tumor characteristics associated with survival.

Material and methods: Patients with esophageal or junctional cancer who underwent induction chemotherapy between 2005 and 2021 were identified from an institutional database of a tertiary referral center. Response to therapy was assessed by (^{18}F-FDG PET)/CT. Response to therapy and treatment options, including surgery or palliation, were discussed in the multidisciplinary tumor board. Overall survival (OS) was calculated using the Kaplan Meier method. Uni- and multivariable analyses were performed to identify prognostic factors for survival.

Results: 238 patients were identified. The majority had esophageal adenocarcinoma (68.9 %) and were treated with a taxane/platinum-based chemotherapy (79.4 %). Response evaluation was performed in 233 patients and 154 of 238 patients (64.7 %) underwent surgical exploration. Resection was performed in 127 patients (53.4 %) resulting in a median and 5-year OS of 26.3 months (95 % CI 18.8–33.8) and 29.6 %, respectively. Presence of T4b (HR = 2.01, 95 % CI 1.02–3.92) and poorly differentiated tumor (HR = 1.45, 95 % CI 1.02–2.10) was associated with worse survival (p = 0.04).

Conclusion: In carefully selected patients with advanced disease not amenable for standard curative treatment, induction chemotherapy followed by esophagectomy may result in a 5-year overall survival of approximately 30 %.

1. Background

Esophageal cancer is a highly lethal malignancy, as reflected by a 5-year survival rate of 40–50 % in patients with non-metastatic locally advanced disease treated with neoadjuvant chemo(radio)therapy followed by esophagectomy [1,2]. However, half of patients present with distant metastases or locoregional advanced disease and are not amenable for curative treatment. In these patients, palliative systemic chemo(-immuno)therapy or local therapy is indicated, resulting in a dismal overall 5-year survival of less than 10 % [3].

In patients with oligometastases or locally advanced disease with poor prognostic characteristics (cN3-category, cT4 tumors) standard curative treatment does not apply. Often these patients also do not fit the criteria of pivotal trials on curative treatment options [1,2]. In these

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patients, induction chemotherapy may be considered. The aim is to downstage the tumor and assesses the biological behavior over a period of time. In selected patients with a favorable response to systemic treatment, surgery with the intention for cure may become an option. Previous low volume retrospective cohort studies suggested that this may be a valid strategy [4–6].

The prospective AIO-FLOT3 study also showed a favorable survival in patients with limited metastatic disease after perioperative chemotherapy (FLOT) and surgery [7]. The role of surgery in patients with oligometastatic disease is currently being studied in the randomized AIO-FLOT5 study [8]. Until then, the role of induction chemotherapy followed by esophagectomy in patients with advanced esophageal cancer outside the criteria for standard treatment is still under discussion.

The aim of this study was to evaluate the outcome of patients treated with induction chemotherapy and to identify patient and/or tumor characteristics associated with long term survival.

2. Material and methods

2.1. Study design

This was a single center, retrospective cohort study, which comprised all patients who were diagnosed with advanced esophageal cancer in the period between 2005-2021 and who underwent induction chemotherapy. As such, the study cohort also included the patients previously described by Toxopeus et al. [6]. Since this was a retrospective study and most patients have died, the need for ethical approval and individual informed consent was waived by the Medical Ethical Committee of the Erasmus MC (MEC-2022-0510).

2.2. Patients

Patients diagnosed with squamous cell- or adenocarcinoma of the esophagus or esophagogastric junction were identified from an institutional database of a tertiary referral center. Patients who underwent induction chemotherapy with response evaluation as advised by the multidisciplinary tumor board (MTB) were included. Induction chemotherapy was only given to fit patients (WHO performance status 0–1) who were diagnosed with incurable disease after complete clinical staging but for whom surgery with curative intent may become an option in case regression of the disease will occur. Indications for induction chemotherapy were the following:

Limited metastatic disease (*i.e.* M1 lymph node metastases and/or limited hematogenous metastases including organ metastases) or an unfavorable T- and N-stage (*i.e.* cN2/N3-disease, cT4 tumor complicated by fistula formation or tumor invasion of aorta or trachea or large primary tumor).

2.3. Clinical staging

Clinical staging was performed using upper endoscopy with biopsies and CT-scan of the thorax and abdomen. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan (^{18}F-FDG PET/CT) was performed in all patients from the year 2012 onwards. When clinically indicated, patients underwent endoscopic ultrasound with fine-needle aspiration of suspicious lymph nodes (EUS-FNA) or a diagnostic laparoscopy or MRI-scan to rule out diffuse (peritoneal) metastases.

2.4. Induction chemotherapy

Induction chemotherapy was given either in our tertiary referral center or in the referring hospital. Different chemotherapy regimens were used including: taxane/platinum doublet chemotherapy, anthracyclin-based triplets, 5-FU based doublets (± trastuzumab) and 5-FU/oxaliplatin/docetaxel (FLOT). Completion of induction chemotherapy was defined as completion of all intended chemotherapy cycles with or without delay or dose reductions due to toxicity.

2.5. Response evaluation

Response assessment was performed by means of an (^{18}F-FDG PET)/CT-scan after completion of all intended cycles of induction chemotherapy and response was classified as ‘complete’ (*i.e.* no residual tumor or metastases visible), ‘partial’ (*i.e.* any decrease of primary tumor and/or metastatic lesions) or ‘stable disease’ (*i.e.* no changes of primary tumor and/or metastatic lesions). Growth of primary tumor and/or metastatic lesions or the emergence of new metastases was classified as ‘progressive disease’. Response to therapy was discussed in the MTB after the (^{18}F-FDG PET)/CT-scan had been performed.

2.6. Surgery

In case of stable disease, partial response or complete response, the MTB established whether patients qualified for radical (R0) resection with curative intent. Surgery was performed by experienced upper GI surgeons. At the start of the operation, sites of potentially irresectable locoregional disease or previously present distant metastases were evaluated by surgical inspection and/or by frozen section analysis of biopsies. If disseminated disease was confirmed by the pathologist or if an R0 resection could not be achieved, no resection was performed. Esophagectomy was performed either via the transthoracic route with gastric conduit reconstruction and cervical or intrathoracic anastomosis or via the transhiatal route with gastric conduit reconstruction and cervical anastomosis.

2.7. Pathology

All resection specimen were staged by specialized upper GI pathologists according to the 7th or 8th UICC TNM classification [9,10]. An R0 resection was defined as no contact between tumor and surgical margin (clearance of 0.0 cm or more). An irradical (R1) resection was defined as contact between tumor cells and the surgical margin [11].

2.8. Follow-up

All patients treated with induction chemotherapy and/or additional esophagectomy underwent standard follow-up according to the local protocol, which comprised of clinical follow-up and (^{18}F-FDG PET)/CT-scan imaging only if complaints were present. At one point in time, February the 23rd 2023, the electronic patient records of all included patients were consulted to estimate survival.

2.9. Study outcomes

The primary outcome was overall survival of all included patients. The secondary outcome was the proportion of patients that proceeded to esophagectomy after induction chemotherapy. Clinical and patient-related factors were also investigated to determine which variables predict survival.

2.10. Statistical analysis

Baseline characteristics were presented as frequencies (percentages) for categorical variables or median with the range for continuous variables. For binominal outcomes, comparisons were made using the Chi-square test and Fisher’s exact test when appropriate. Survival was calculated from date of diagnosis until date of death or date of last follow-up. The probability of survival over time was calculated using the Kaplan-Meier method. The proportion of patients that proceeded to surgery was calculated relative to all patients treated with induction chemotherapy. Univariable and multivariable cox regression analyses

was used to determine which variables predict survival, including age, gender, tumor histology, tumor differentiation grade and clinical T- and N-category. All variables with p-value <0.05 in univariable analysis were included in multivariable cox regression analysis. Data were expressed as hazard ratio's (HR) with 95 % confidence intervals (CI). Statistical significance was defined as p-value <0.05. Statistical analysis was performed using R version 4.0.4 (www.r-project.org).

3. Results

3.1. Patients

Between January 2005 and December 2021, 238 patients were diagnosed with esophageal or junctional cancer. Baseline characteristics are presented in Table 1.

3.2. IQR: interquartile range

Indications for induction chemotherapy included wide-spread N2 (*i.e.* lymph node metastases with too long intervening distance for irradiation therapy)/N3 disease (115 of 238 patients; 48.3 %), irresectable disease (cT4 or irresectable lymph nodes) (60 of 238 patients; 25.2 %), lymphatic oligometastatic disease (43 of 238 patients; 18.1 %) or hematogenous oligometastatic disease (20 of 238 patients; 8.4 %). The majority of patients was treated with taxane/platinum based chemotherapy (189 of 238 patients; 79.4 %) followed by anthracyclin-based triplets (20 of 238 patients; 8.4 %), 5-FU based doublets (± trastuzumab) (14 of 238 patients; 5.9 %) or FLOT (15 of 238 patients; 6.3 %). All chemotherapy cycles, including those with one or more postponed cycles, were completed in 79 % of patients.

Three patients died before the response evaluation was performed and two patients became unfit for surgery, resulting in 233 patients who underwent response assessment (Table 2). Surgery was indicated in 154 patients and 61 patients (26.2 %) received palliative care. Esophagectomy was finally performed in 127 patients (54.5 %) as some patients declined surgery, were lost to follow-up or did not proceed to resection because of an irresectable tumor or distant metastases (Fig. 1). Pathological tumor characteristics of the patients that underwent resection are shown in Table 3. Fifteen of 127 patients (11.8 %) had a pathologically complete response (ypT0N0). Some 101 of 127 patients (79.5 %) had tumor-free resection margins.

Table 1
Patient and tumor characteristics.

Characteristics	All patients, n = 238 (%)
Sex	
Male	179 (75.2)
Age (median [IQR])	62 (56–59)
Tumor type	
Adenocarcinoma	164 (68.9)
Squamous cell carcinoma	74 (31.3)
Tumor location	
Proximal/middle esophagus	56 (23.5)
Distal esophagus/EGJ	182 (76.5)
Differentiation grade	
Well differentiated (G1)	10 (4.2)
Moderately differentiated (G2)	62 (26.1)
Poor differentiated (G3)	92 (38.7)
Undifferentiated (G4)	1 (0.4)
Differentiation grade cannot be assessed (Gx)	73 (30.7)
Clinical T-category	
cT2	5 (2.1)
cT3	159 (66.8)
cT4a	13 (5.5)
cT4b	22 (9.2)
cTx	19 (8.0)
Clinical N-category	
cN0	13 (5.5)
cN1	51 (21.4)
cN2	109 (45.8)
cN3	49 (20.6)
cNx	16 (6.7)
Clinical M-category	
cM0	160 (67.2)
cM1	69 (29.0)
cMx	9 (3.8)

Table 2
Response to induction chemotherapy.

	Clinical N2/N3 disease, n = 114 (%)	Irresectable disease, n = 56 (%)	Oligometastases lymphatic, n = 43 (%)	Oligometastases hematogenous, n = 20 (%)
Response to therapy				
Complete response	1 [1]	–	2 [5]	1 [5]
Partial response	88 (77)	35 (63)	34 (79)	13 (65)
Stable disease	12 [10]	7 [13]	–	4 [20]
Progressive disease	13 [11]	14 [25]	7 [16]	2 [10]

The median OS of the total group was 17.4 months (95 % CI 14.9–19.8). Partial response or stable disease was seen in 65 patients who did not undergo surgery. The median OS of these patients was 14.1 months (95 % CI 10.8–17.4).

The estimated 5-year OS rate for patients who underwent esophagectomy was 29.6 % (median OS 26.3 months, 95 % CI 18.8–33.8). Median OS of patients who underwent R0 resection was 36.7 months (95 % CI 27.6–57.1), compared to 15.1 months (95 % CI 12.7–17.4) for patients with a R1 resection. The 5-year OS rate of patients with a pathological complete response was 60 %.

Univariable analysis of prognostic factors showed that cT4b (HR = 2.01, 95 % CI 1.02–3.92, p = 0.04) and poor differentiation grade (HR = 1.45, 95 % CI 1.02–2.01, p = 0.04) were significantly associated with worse survival and both remained significant after multivariable analysis (HR = 2.21, 95 % CI 1.12–4.36, p = 0.02 vs. HR = 1.52, 95 % CI 1.07–2.16, p = 0.02) (Table 4).

4. Discussion

In selected patients with advanced disease not amenable for standard neoadjuvant treatment, induction chemotherapy followed by surgery may lead to a 5-year overall survival of 30 %. This is better than the 2–26 % 5-year overall survival of patients with stage III-IV esophageal cancer as reported in the Netherlands' Cancer Registry [3]. Selection of patients that should be referred for surgery is difficult and largely depends on response to induction chemotherapy and the estimated probability to completely resect the tumor with microscopic negative margins.

To our knowledge, this is one of the largest retrospective studies on survival of patients treated with induction chemotherapy worldwide. Patients with different indications for induction chemotherapy were included, but the majority had extensive disease or oligometastases. The CROSS trial included patients with locoregional advanced disease (*i.e.* cT1N1M0 or cT2-3N0-1M0) and tumor length and width not exceeding 8 cm and 5 cm, respectively. The outcomes of patients in our cohort should not be compared to patients from the CROSS trial as it concerns a completely different patient population [12]. A recent study investigated the efficacy of CROSS in patients outside the inclusion/exclusion criteria of the original trial report [13]. This study showed that tumors >8 cm in length or >5 cm in width had poorer recurrence-free survival (HR = 2.06, 95 % CI 0.99–4.27, p = 0.052) and the presence of celiac nodal metastases was associated with poor outcomes. This supports the argument to consider induction chemotherapy in those patients with locoregional disease beyond the CROSS criteria.

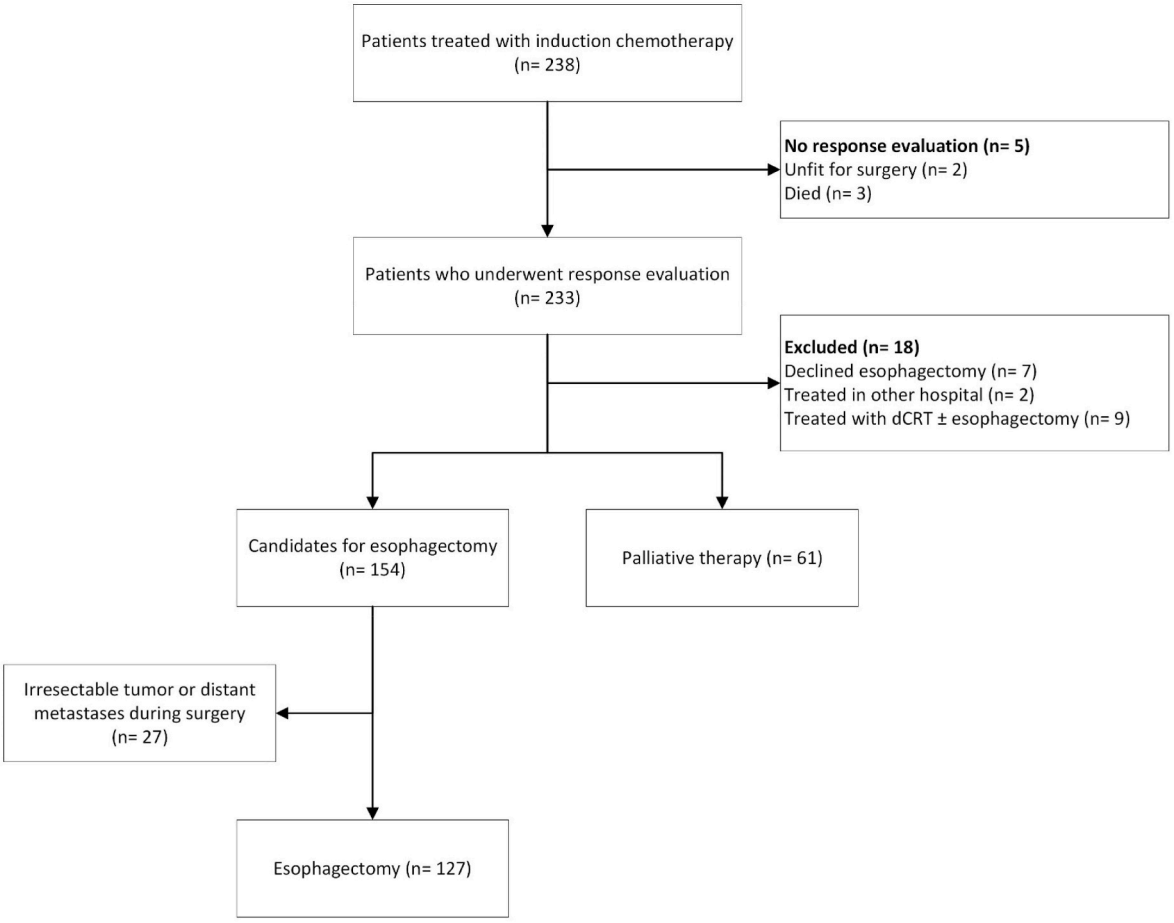

Fig. 1. Flowchart of patients who underwent response evaluation and either palliative care or esophagectomy after induction chemotherapy.

When comparing the OS of our study to patients with limited metastatic gastric cancer in the AIO-FLOT3 trial, better median OS for all patients and patients who underwent esophagectomy was seen in the trial, respectively 22.9 and 31.3 months [7]. The high OS rates in the AIO-FLOT3 trial can be a result of patient selection and the strict criteria for trial participation. The literature shows 5-year OS rates ranging from 1 to 17 % for stage III-IV gastric cancer [3].

Patients in our study were categorized according to the indications for induction chemotherapy. Various definitions for oligometastatic disease are used which complicates the comparison of results between studies. Initiatives such as the '*OligoMetastatic Esophagogastric Cancer*' (OMEC) project may help in getting consensus on the definition, diagnostic criteria and treatment for oligometastatic esophagogastric cancer including the initiation of pan-European multinational studies to look for novel strategies to improve survival [14–16].

Therapies that target specific tumour drivers or immune checkpoints are increasingly explored for patients with metastatic esophageal cancer. Nowadays, patients are eligible for immunotherapy in addition to chemotherapy in case of high PD-L1 expression, which may improve response to therapy and prolong overall survival. Furthermore, the recent Checkmate and KEYNOTE studies have provided us with phase-III data on 5-FU containing doublets in metastatic adenocarcinoma and squamous cell carcinoma of the esophagus, indications for which historically, limited data on the optimal palliative treatment were available [17]. In the induction setting, the focus often lies on the anti-tumor regimen with the highest chance of tumor response. In that respect, one could consider FLOT or a 5-FU containing doublet with trastuzumab for (HER2-positive) adenocarcinoma, as response to FLOT was 60 % in the AIO-FLOT3 trial and response to trastuzumab plus chemotherapy was 47 % in the TOGA trial [7,18]. For squamous cell carcinoma, based on the KEYNOTE-590 and the Checkmate-648, response rates were highest for patients treated with pembrolizumab or nivolumab plus chemotherapy, 43–53 %, especially in the PD-L1 positive population [19,20]. In this cohort, patients were often treated with carboplatin/paclitaxel based on a response rate of 43 % in phase-II, mild toxicity profile and extensive local experience with this regimen [21].

The Neo-AEGIS study showed that perioperative chemotherapy is non-inferior to CROSS chemoradiotherapy for patients with locally advanced esophageal cancer, but CROSS resulted in better local tumor response (*i.e.* higher R0 resection rate and tumor regression grade) [22]. One could argue that chemoradiotherapy could improve locoregional control in addiyion to induction chemotherapy [23]. In fact, the TNT-OES-1 trial is investigating the safety and feasibility of combined systemic (FLOT) and locoregional (CROSS) therapy for esophageal oligometastatic adenocarcinoma [24]. If patients are able to complete and tolerate such dual therapy, this sequential combination can be promising for those patients with esophageal cancer not amenable for standard treatment.

An important strength of our study was the number of included patients who were treated with induction chemotherapy and this report can be helpful to indicate which patients may benefit from this strategy.

As limitation, this was a retrospective study of data obtained from electronic patient records and therefore some data were missing or incomplete (*e.g.* completion rate of induction chemotherapy and tolerance to chemotherapy). Tumor regression grade and WHO performance status were not reported for most patients and therefore could not be included in the cox regression analysis, even though these factors are important according to current literature. Immortal time bias is present,

Table 3
Pathology of the resection specimen *Survival*.

Characteristics	All patients, n (%)
Tumor type	
Adenocarcinoma	85 (66.9)
Squamous cell carcinoma	18 (14.2)
High grade dysplasia	2 (1.6)
No tumor present	15 (11.8)
Unknown	7 (5.5)
Differentiation grade	
Well differentiated (G1)	11 (8.7)
Moderately differentiated (G2)	35 (27.6)
Poor differentiated (G3)	54 (42.5)
Differentiation grade cannot be assessed (Gx)	27 (21.3)
Pathological T-category	
ypT0	20 (15.7)
ypTis	2 (1.6)
ypT1	10 (7.9)
ypT2	22 (17.3)
ypT3	72 (56.7)
ypT4	1 (0.8)
Pathological N-category	
ypN0	39 (30.7)
ypN1	49 (38.6)
ypN2	22 (17.3)
ypN3	16 (12.6)
ypNx	1 (0.8)
Pathological M-category	
ypM0	76 (59.8)
ypM1	15 (11.8)
ypMx	36 (28.3)
Radicality	
R0 resection	101 (79.5)
R1 resection	26 (20.5)

since data were missing of the first date of induction chemotherapy. Therefore, it was only possible to calculate the OS from date of diagnosis. Besides that, the data of this study represent a selected cohort of patients who qualify for induction chemotherapy based on patient and tumor characteristics, which leads to selection bias. Moreover, this study describes the results of a single center and includes a heterogeneous population which may jeopardize internal and external validity. Patients were treated with different chemotherapy regimens, which also makes it difficult to compare the results across studies. Finally, some patients underwent FDG-PET/CT and some only underwent a conventional CT-scan to evaluate response to therapy. This may have underestimated the rate of detected distant metastases preoperatively, since we know that FDG-PET/CT is able to detect distant metastases in 8–10 % of patients after neoadjuvant therapy [25–27].

Despite these limitations, this retrospective cohort study of patients treated with induction chemotherapy provides insight into survival of this specific population. Randomized trials are awaited to evaluate whether esophagectomy may be of benefit in patients with limited metastatic esophageal cancer, and whether induction chemotherapy may be of benefit before chemoradiotherapy and/or esophagectomy in patients with very locally advanced tumors.

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Declaration of interest

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Table 4
Univariable and multivariable cox regression analysis for survival after induction chemotherapy.

	Univariable analysis, HR (95 % CI)	*p-value*	Multivariable analysis, HR (95 % CI)	*p-value*
Gender				
Male	1			
Female	1.23 (0.89–1.70)	0.20		
Age	1.01 (0.99–1.03)	0.06		
Histology				
Squamous cell carcinoma	1			
Adenocarcinoma	0.94 (0.69–1.27)	0.67		
Tumor differentiation grade				
Good/moderately differentiated (G1-2)	1			
Poorly differentiated (G3)	1.45 (1.02–2.10)	0.04	1.52 (1.07–2.16)	0.02
Undifferentiated (G4)	1.65 (0.23–12.0)	0.62	1.82 (0.25–13.26)	0.55
Differentiation grade cannot be assessed (Gx)	1.33 (0.92–1.92)	0.14	1.30 (0.90–1.89)	0.16
Clinical T-category				
cTx	1			
cT2	1.39 (0.46–4.18)	0.56	1.32 (0.44–4.01)	0.62
cT3	0.89 (0.52–1.52)	0.67	0.92 (0.54–1.58)	0.77
cT4	0.92 (0.40–2.01)	0.84	0.93 (0.41–2.14)	0.87
cT4a	0.96 (0.48–1.93)	0.91	1.02 (0.51–2.05)	0.96
cT4b	2.01 (1.02–3.92)	0.04	2.21 (1.12–4.36)	0.02
Clinical N-category				
cN0	1			
cN1	0.61 (0.31–1.22)	0.16		
cN2	0.68 (0.35–1.30)	0.24		
cN3	0.69 (0.34–1.37)	0.29		
cNx	0.71 (0.32–1.61)	0.41		

HR: hazard ratio; CI: confidence interval.

All remaining authors declared to have no conflicts of interest.

CRediT authorship contribution statement

Charlène J. van der Zijden: Study concepts, Study design, Funding acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript review. **Pieter C. van der Sluis:** Manuscript review. **Bianca Mostert:** Study design, Quality control of data and algorithms, Data analysis and interpretation, Manuscript editing. **Joost J.M.E. Nuyttens:** Manuscript review. **Manon C.W. Spaander:** Manuscript review. **Eelke L.A. Toxopeus:** Manuscript review. **Roelf Valkema:** Manuscript review. **Laurens V. Beerepoot:** Manuscript review. **Henk K. van Halteren:** Manuscript review. **Sjoerd M. Lagarde:** Study design, Data analysis and interpretation, Manuscript editing, Manuscript review. **Bas P.L. Wijnhoven:** Study concepts, Study design, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript review.

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