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Patterns of recurrence following definitive chemoradiation for patients with proximal esophageal cancer

J. de Vos-Geelen [a, *], S.M.E. Geurts [a], G.A.P. Nieuwenhuijzen [b], F.E.M. Voncken [c], J.A. Bogers [d], P.M. Braam [e], C.T. Muijs [f], M.A. de Jong [g], N. Kasperts [h], T. Rozema [i], G.J. Blom [j], S.A.W. Bouwense [k], L.B.J. Valkenburg-van Iersel [a], P.M. Jeene [l, m], F.J.P. Hoebers [n, 1], V.C.G. Tjan-Heijnen [a, 1]

[a] Dept. of Internal Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center, P.O. box 5800, 6202, AZ, Maastricht, the Netherlands
[b] Dept. of Surgery, Catharina Hospital Eindhoven, P.O. box 1350, 5602, ZA, Eindhoven, the Netherlands
[c] Dept. of Radiation Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, P.O. box 90203, 1006, BE, Amsterdam, the Netherlands
[d] Radiotherapiegroep Arnhem, P.O. box 60160, 6800, JD, Arnhem, the Netherlands
[e] Dept. of Radiotherapy, RadboudUMC, P.O. box 9101, 6500, HB, Nijmegen, the Netherlands
[f] Dept. of Radiation Oncology, University Medical Center Groningen, University of Groningen, P.O. box 11120, 9700, RB, Groningen, the Netherlands
[g] Dept. of Clinical Oncology, Leiden University Medical Centre, P.O. box 9699, 2300, RC, Leiden, the Netherlands
[h] Dept. of Radiotherapy, University Medical Center Utrecht, P.O. box 85500, 3508, GA, Utrecht, the Netherlands
[i] Insituut Verbeeten, P.O. box 90120, 5000, LA, Tilburg, the Netherlands
[j] Dept. of Radiation Oncology, Amsterdam University Medical Centers, VU University, P.O. box 7057, 1007, MB, Amsterdam, the Netherlands
[k] Dept. of Surgery, Maastricht University Medical Center, P.O. box 5800, 6202, AZ, Maastricht, the Netherlands
[l] Dept. of Radiotherapy, Amsterdam University Medical Centers, University of Amsterdam, P.O. box 22660, 1100, DD, Amsterdam, the Netherlands
[m] Radiotherapiegroep Deventer, P.O. box 123, 7400, AC, Deventer, the Netherlands
[n] Dept. of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, P.O. box 3035, 6202, NA, Maastricht, the Netherlands

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ABSTRACT

Introduction: The aim of this retrospective study was to determine the patterns of recurrence and overall survival (OS) in patients achieving clinical complete response after treatment with definitive chemoradiation (CRT) for proximal esophageal cancer.
Materials and methods: Patients with proximal esophageal cancer treated with CRT between 2004 and 2014 in 11 centers in the Netherlands were included. OS and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Cumulative incidence of first recurrence (locoregional or distant) and locoregional recurrence (LRR) were assessed using competing risk analyses.
Results: In 197 of the 200 identified patients, response was evaluated, 133 (68%) showed a complete response. In complete responders, median OS, three-year OS, and PFS were 45.0 months (95% CI 34.8–61.5 months), 58% (95% CI 48–66), and 49% (95% CI 40–57), respectively. Three- and five-year risk of recurrence were respectively 40% (95% CI 31–48), and 45% (95% CI 36–54). Three- and five-year risk of LRR were 26% (95% CI 19–33), and 30% (95% CI 22–38). Eight of 32 patients with an isolated LRR underwent salvage surgery, with a median OS of 32.0 months (95% CI 6.8-not reached).
Conclusion: In patients with a complete response after definitive CRT for proximal esophageal cancer, most recurrences were locoregional and developed within the first three years after CRT. These findings suggest to shorten locoregional follow-up from five to three years.

* Corresponding author. Dept. of Internal Medicine, Div. of Medical Oncology, Maastricht University Medical Center, P.O. box 5800, 6202, AZ, Maastricht, the Netherlands.
E-mail address: judith.de.vos@mumc.nl (J. de Vos-Geelen).
[1] These authors share senior authorship.

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Introduction

Definitive chemoradiation (CRT) is the standard of care for patients with a proximal esophageal squamous cell cancer (SCC), recommended by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) guidelines [1–3].

Prognosis of proximal esophageal cancer (EC) is poor, providing three-year overall survival (OS) rates in patients treated with CRT of about 35–45% [4–11]. Our previous retrospective cohort study showed comparable OS between four different CRT regimens including cisplatin or carboplatin and paclitaxel backbones and low (≤50.4 Gy) or high dose (>50.4 Gy) radiotherapy (RT) [12]. Long-term survival is only achieved in complete responders to CRT [7,9,13,14]. In the absence of clinical complete response (CR), none of the patients were alive at three years following CRT [7,9], whereas three-year OS rates were shown to be approximately 25% in patients treated with salvage surgery for residual or progressive disease [13,14]. However, additional surgical resection independent of response following CRT was not associated with a survival benefit [14].

Patterns and treatment of recurrence in complete responders to definitive CRT for proximal EC are currently unknown, hindering evidence-based follow-up and clinical counseling of these patients. Whether or not follow-up after definitive CRT for EC is useful remains controversial. Hence, recommendations by NCCN and ESMO guidelines are inconsistent regarding follow-up strategies and duration of surveillance [1,3].

The purpose of this study was to determine patterns of recurrence, treatment and OS in patients who achieved CR following definitive CRT for proximal EC.

Materials and methods

This multicenter, retrospective, observational study was conducted in 11 centers in The Netherlands. Patients were identified in site-specific databases, complemented with the Netherlands Cancer Registry, a population-based cancer registry of all newly diagnosed malignancies in the Netherlands. We identified 200 consecutive patients who underwent definitive CRT for proximal EC, from January 2004 to December 2014 [15]. All patients had histologically confirmed SCC of the proximal esophagus, with maximum distal extension up to 24 cm of the incisors, in which supraclavicular nodal involvement was allowed. Tumor staging was performed according to the Union for International Cancer Control TNM classification that was valid at the time of diagnosis. Since the TNM classification did not essentially change, no coding was performed to a uniform TNM version, except nodal status which was converted into N1 excluding subdivision of N1/2/3. Further information on the study protocol was described previously [15].

Patients were generally examined through physical examination and history taking in regular follow-up according to national guidelines at four to eight weeks after completion of CRT, and every three months in the first year, with escalating interval up to five years or until death. Endoscopy and imaging was performed in case of signs or symptoms of recurrence. No strict imaging protocol for follow-up was established. CR following CRT was defined as no clinical or radiological evidence of locoregional disease three months after completing CRT as defined by the treating physician.

Patient informed consent was waived by the Medical Ethics Board azM/UM due to the retrospective nature of the study (METC 15-4-012). The study was approved by the scientific committee of the Dutch Upper GI Cancer Group (DUCG), and the Dutch Head and Neck Oncology Cooperative Group (NWHHT 2017–01).

Data collection

Patient demographics, tumor characteristics, treatment details, and vital status were collected retrospectively from the medical records, obtained by trained registry clerks. Data collection took place between April 2017 and May 2018.

Outcomes

In the total group, we aimed to determine OS stratified by response. In the complete responders, additional endpoints were progression-free survival (PFS), cumulative incidence of first recurrence (locoregional or distant), and cumulative incidence of locoregional recurrence (LRR) as first event. Furthermore, we examined whether potential prognostic factors (age, sex, WHO performance status, comorbidity, clinical lymph node (cN) status, tumor location, gross tumor volume (GTV), and radiation dose) were associated with OS in CR.

LRR was classified as recurrence located at the site of the primary tumor and/or regional lymph nodes, up to supraclavicular nodes. The sites of LRR were assessed in relation to the radiation fields and scored as infield or outfield. Distant recurrence was defined as evidence of disease in any other site. The date of recurrence was taken as the date of confirmed histology (if present) or date of imaging of recurrent disease. Diagnostics and treatment modalities of recurrent disease were assessed.

Statistical analysis

Differences between continuous and categorical variables were tested using the Mann-Witney U and Chi-square test, respectively. OS was calculated from the start of CRT to date of death. For the patients with an isolated LRR, OS was additionally calculated from detection of recurrence. PFS was defined as the start of CRT to the date of recurrence or death. Time to recurrence was calculated from the start of CRT until the occurrence of LRR or distant metastasis, whichever came first, with interoccurring death as competing event. Time to LRR was calculated from the start of CRT to the date of LRR diagnosis, considering interocurring distant metastasis and death as competing events. For all time to event analyses, censoring occurred at last contact. OS and PFS were calculated using the Kaplan-Meier method. Cumulative incidence of recurrence and LRR were assessed using competing risk analyses. Median follow-up was calculated using the inverse Kaplan-Meier method for OS (death censored). A full multivariable model of potential predictors for OS was conducted using Cox regression analysis. Multiple imputation was used for missing data. Presence of multicollinearity was checked using variation inflation factors.

Results

A total of 200 patients were included, of whom 133 patients (67%) achieved a complete response (CR), 42 (21%) a partial response, and 17 (9%) stable disease following definitive CRT. Five patients (3%) had progressive disease, and in three patients (2%) response could not be evaluated.

In complete responders, median age at time of diagnosis was 64 years (range, 42–85 years) (Table 1). Male sex and good performance status, i.e. WHO 0 or 1, were predominant. Median radiation dose of the primary treatment was 50.4 Gy. CRT was completed as planned in 106 patients (80%). Median follow-up was 64.7 months (95% CI 47.8–81.7).

Table 1
Baseline and tumor characteristics of 133 complete responders following chemoradiation for proximal esophageal cancer.

Characteristic	Complete responders N = 133 No.	%
Age		
Median, years (range)	64 (42-85)	
≥70 years	33	25
Sex		
Male	82	62
WHO performance score		
0-1	118	89
2-3	6	5
Unknown	9	7
Pre-diagnostic weight loss		
<5%	55	41
5–10%	25	19
>10%	26	20
Unknown	27	20
Comorbidity		
Any	75	56
Cardiovascular disease	40	30
Pulmonary disease	9	7
Previous malignancy	23	17
None	58	44
Tumor location		
Cervical (<18 cm)	41	31
Upper thoracic (18–24 cm)	92	69
Tumor length		
Median, cm (range)	4 (1-15)	
Obstruction or unknown	38	29
Tumor grade		
G1-2	41	31
G3	28	21
Gx	64	48
Clinical T stage		
cT1-3	85	64
cT4	35	26
cTx	13	10
Clinical N stage		
cN0	46	35
cN+	85	64
cNx	2	2
Chemoradiation regimen		
Cisplatin, RT > 43.2 and ≤ 50.4 Gy	32	24
Cisplatin, RT > 50.4 Gy	27	20
Carboplatin, Paclitaxel, RT > 43.2 and ≤ 50.4 Gy	65	49
Carboplatin, Paclitaxel, RT > 50.4 Gy	9	7
GTV		
Median, cm3 (range)	33.0 (2.4-119.1)	
IQR	19.0–49.1	
Unknown	31	23
Radiation dose		
Median, Gy (range)	50.4 (48.6-70.0)	
Chemoradiation completed as planned		
Yes	106	80
No	21	16
Unknown	6	5

GTV, gross tumor volume: the volume of the macroscopic tumor in cm^3 as defined by the tumor-delineation on the RT planning-CT scan; IQR, interquartile range. Percentages may not add up to 100 because of rounding.

Overall survival

Median OS was 45.0 months (95% CI 34.8–61.5 months) and three-year OS was 58% (95% CI 48%–66%) (Supplementary Figure A1). Neither age, sex, comorbidity, lymph node status, GTV, nor radiation dose were significant prognostic factors for OS, whereas WHO performance status and tumor location were identified as clinically important factors with borderline significance (Table 2).

Table 2
Multivariable comparison of prognostic factors influencing overall survival in complete responders (N = 133) following chemoradiation for proximal esophageal cancer.

	HR (95%CI)	P value
Age at diagnosis	1.00 (0.97-1.04)	0.84
Sex		
Male	Ref.	
Female	0.67 (0.39-1.15)	0.15
WHO performance status		
0–1	Ref.	
2–3	2.62 (0.90-7.63)	0.08
Comorbidity		
No	Ref.	
Yes	0.84 (0.50-1.40)	0.50
cN stage		
N0	Ref.	
N+	1.19 (0.73-1.96)	0.48
Tumor location		
Cervical	Ref.	
Upper thoracic	0.64 (0.38-1.07)	0.09
GTV (tertiles), cm3		
≤25	Ref.	
25–43	1.04 (0.56-1.94)	0.90
>43	1.64 (0.91-2.97)	0.10
Radiation dose, Gy		
≤50.4	Ref.	
>50.4	1.10 (0.66-1.82)	0.72

GTV, gross tumor volume: the volume of the macroscopic tumor in cm^3 as defined by the tumor-delineation on the radiotherapy planning-CT scan.

Recurrence

Of the 133 patients with a CR, 58 patients had recurrent disease, of whom 32 (55%) had an isolated LRR, 19 (33%) distant metastases only, and seven (12%) concurrent locoregional and distant recurrences as first site (Fig. 1).

Three-year PFS was 49% (95% CI 40%–57%). Three- and five-year incidences of any recurrence (locoregional or distant) was 40% (95% CI 31%–48%) and 45% (95% CI 36%–54%) and for LRR 26% (95% CI 19–33) and 30% (95% CI 22–38), respectively (Fig. 2).

Among the patients with LRR, distribution predominantly showed recurrence primarily infield at the original tumor site, followed by infield at the lymph node site (Fig. 1). Metastatic disease manifested at a single site in ten patients, and at multiple sites in 16 patients. The lungs were the main site of metastatic disease (N = 22), followed by distant lymph nodes (N = 9), bone (N = 8), brain (N = 4), and liver (N = 3).

Of the patients with LRR, 29 patients (74%) were symptomatic at presentation and in 31 patients (80%) LRR were pathologically confirmed (Supplementary Table A1). Fourteen patients (54%) who developed distant metastasis showed physical complaints. Distant failures were pathologically confirmed in six patients (22%).

Twenty patients developed a second primary tumor, mainly located in the head and neck (N = 7), lung (N = 4), and esophagus (N = 3).

Among the 32 patients with an isolated LRR, 8 (25%) underwent salvage surgery, 16 (50%) re-irradiation, 3 (9%) chemotherapy, and 8 (25%) best supportive care only. Salvage surgery included esophageal resection and gastric conduit (N = 6), cervical lymph node dissection (N = 1), and radiofrequency ablation (N = 1). Of the patients undergoing surgery for their recurrence, four received multimodal treatment with RT (N = 3) or CRT (N = 1). Median radiation dose to treat LRR was 30 Gy (range 12–50.4 Gy).

Median OS of patients undergoing salvage surgery for isolated LRR was 50.6 months (95% CI 31.2–70.0, three- and five-year OS 75% and 30%) from the start of CRT at primary diagnosis. Median OS from detection of LRR was 32.0 months (95% CI 6.8-not reached,

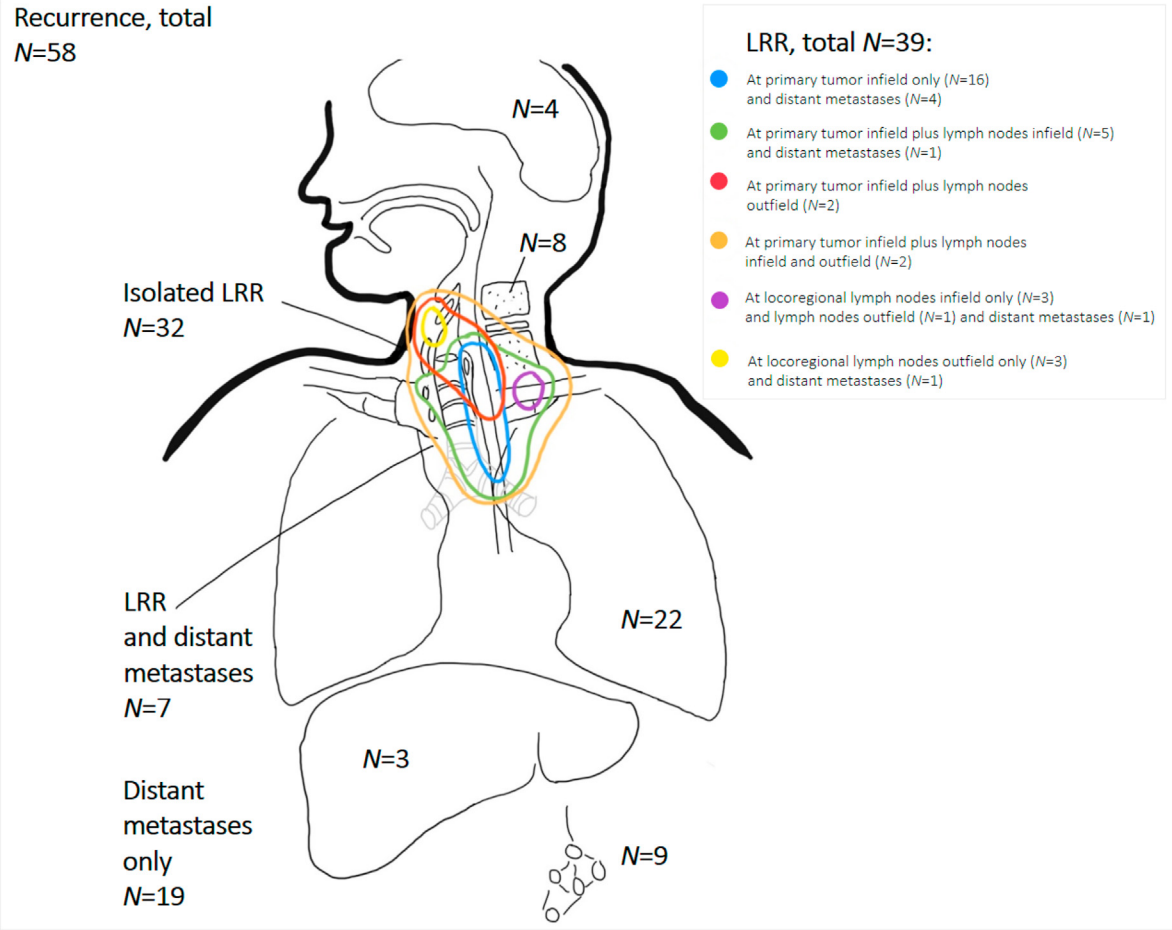

Fig. 1. Location of first recurrence in complete responders following chemoradiation for proximal esophageal cancer.
LRR, locoregional recurrence.

three- and five-year OS 44% and 29%) for salvage surgery, 8.7 months for patients undergoing re-irradiation with or without chemotherapy, 3.0 months for chemotherapy alone, and 1.5 months for best supportive care only (Supplementary Figure A2). At the end of follow-up, five patients had died following salvage surgery, all as a result of recurrent disease. Timing of detection of LRR in patients undergoing salvage surgery compared with those patients with LRR only who were unable to undergo surgery for LRR did not differ (Supplementary Figure A3).

In metastatic disease (with or without LRR), three patients (12%) underwent a metastasectomy (with or without RT). Their median OS from detection of recurrence was 16.0 months. Four patients (15%) underwent chemotherapy (with or without RT) with a median OS of 7.0 months. A variety of chemotherapeutic agents were administered in recurrent disease, mostly fluoropyrimidine-based. RT only was applied in five patients with a median radiation dose of 22.8 Gy (range 18–39 Gy), demonstrating a median OS of 7.6 months. Median OS for patients not receiving antitumor treatment (N = 14) was 3.5 months.

Discussion

This retrospective cohort study demonstrated that most recurrences in complete responders following CRT for proximal EC were locoregional and occurred mainly in the primary involved tumor field within the first three years. In most cases of LRR local therapy was applied, i.e. salvage surgery or second course RT. Only one out of five patients with either a locoregional or distant recurrence received chemotherapy.

To the best of our knowledge, this is the largest cohort reporting the pattern of recurrence in complete responders after CRT for proximal EC, observing a three- and five-year risk of recurrence of 40% and 45%. Two-thirds of all recurrences were locoregional failures, which was in line with previous cohorts in proximal EC, reporting LRR in 58–84% of the recurrences after CRT although not specific for CR [4,5,8,14,16,17], except for a small Canadian cohort of complete responders (N = 38) [4].

The high rate of LRR after CRT emphasizes consideration of improvement in local therapy. However, adjuvant resection after CRT did not prolong survival in cervical EC compared with definitive CRT alone in an Italian cohort study [14]. Nonetheless, randomized data are lacking.

Locoregional recurrences were mainly within the RT field, suggesting a potential benefit of escalating radiation dose. However, previous studies showed inconsistent results of dose escalation. A recent meta-analysis including ten observational studies (N = 4918), and one small prospective trial (N = 28), suggested that a higher radiation dose to the primary tumor volume was associated with better locoregional failure free survival [18]. However, the recent phase III dose escalation ARTDECO study in EC randomizing 260 patients (61% SCC), demonstrated that radiation dose escalation up to 61.6 Gy versus 50.4 Gy to the primary tumor did not improve local control [19].

Salvage surgery in case of an isolated LRR could be considered

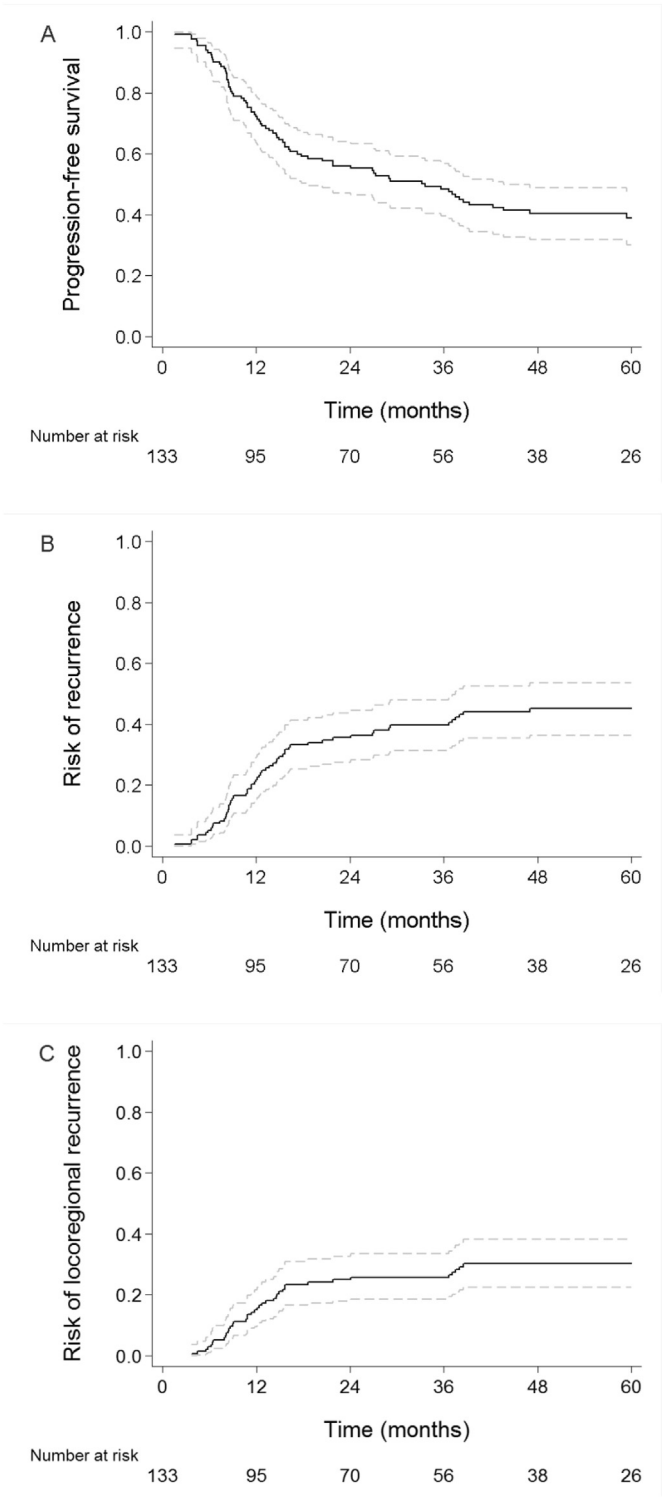

Fig. 2. Progression-free survival (A), cumulative incidence of recurrence (locoregional or distant) (B), and cumulative incidence of locoregional recurrence as first event (C) for patients with complete response following chemoradiation for proximal esophageal cancer.
Dashed lines correspond with the 95% confidence intervals.

for highly selected patients. In our study eight out of 32 patients (25%) with LRR only underwent salvage surgery, of which 44% were alive at three years after detection of recurrence. These results are comparable with a Japanese phase II trial including five patients (38%) with LRR of cervical EC who underwent surgery, of which three remained alive for more than three years [13]. Schieman et al. demonstrated corresponding outcomes, with a three-year OS rate of 33% [20]. The reported long-term survival following salvage surgery was confirmed in retrospective studies including patients with cancers of the esophagus, i.e. proximal, mid or distal, treated with definitive CRT and experiencing a LRR [21,22]. Moreover, recurrences in the proximal part of the esophagus are even more difficult to treat due to long-term side effects after definitive CRT, e.g. strictures and fistulas [23–25]. Hence, most patients suffering from a LRR following CRT for proximal EC are unable to undergo salvage surgery. Although a durable survival can be achieved in this group, salvage esophagectomy should be thoughtfully balanced with perioperative morbidity and mortality of such challenging resections by both patients and physicians [21,22].

The role of re-irradiation in LRR following definitive CRT in EC is controversial. In the current study, re-irradiation was carried out in 16 patients with an isolated LRR, with a median radiation dose of 30 Gy (range 12–50.4 Gy). Median OS of patients undergoing salvage RT was 8.7 months from the point of detection of locoregional disease. Literature on re-irradiation in EC is sparse. Zhou et al. retrospectively analyzed 55 patients with recurrences treated with salvage RT with a median dose of 54 Gy (range 18–66 Gy), demonstrating a median OS of five months [26]. A recent Chinese study established long-term survival of 17 months in patients treated with re-irradiation for locoregional recurrent esophageal SCC [27]. Others found comparable poor outcomes following re-irradiation [28,29]. Hence, only in selected and highly motivated patients a radical radiotherapeutic approach can be considered, outweighing the significant risks of re-irradiation, e.g. fistulation, stenosis, and vascular blow-out.

Although the minority of initial recurrences in our study were distant, improvements in systemic therapy remain warranted, regarding optimization of systemic cytotoxic effects in recurrent disease, but also for synergistic effects in primary CRT. The implementation of immunotherapy in metastatic EC is to be awaited, after proved safety and efficacy of the ATTRACTION-3, CheckMate-649, and KEYNOTE-590 trials, especially in the subset of programmed death ligand-1 positive tumors [30–32]. Furthermore, the adjuvant CheckMate-577 trial showed a significantly improved disease-free survival with adjuvant nivolumab compared with placebo in patients with resected EC after neoadjuvant chemoradiation and have not achieved a pathological complete response [33]. In addition, a phase II study is assessing the efficacy of atezolizumab following definitive CRT to increase CR rate [34].

In the current study, main metastatic sites were lung and lymph nodes, comparable with the results from smaller observational studies [8,35,36]. In our cohort, only 15% of patients developing distant metastases received palliative chemotherapy. This corresponds to historical data in a large cohort of proximal EC [37], and reflects the limited high level evidence of palliative systemic therapy in metastatic esophageal SCC [38], as well as the frailty of this population.

The approach regarding evaluation of response after CRT has not been established. ESMO guidelines do not include recommendations concerning response evaluation following definitive CRT [3]. However, the NCCN guideline committee recommends endoscopy and biopsy [1]. Others have suggested a role for 18F-FDG PET/CT, diffusion-weighted MRI [39] or molecular biomarkers, such as circulating tumor DNA [40] for response evaluation, which has to be explored in future studies. The potential benefits of such extensive assessments have to outweigh the impact on either patients and healthcare facilities.

Systematic surveillance strategies after successful definitive treatment for proximal EC remain controversial. We demonstrated

that most patients presented with symptoms at the time of recurrence, which was expected since Dutch esophageal and head and neck cancer guidelines, as well as NCCN guidelines [1], advice symptom-based follow-up, whereas endoscopy and imaging studies are only recommended to be performed on indication. In contrast, ESMO guideline states that a three-month follow-up based on endoscopy, biopsies and CT scan may be recommended in the case of CR to definitive CRT. It might be expected that a more vigorous approach of follow-up will lead to an earlier detection of recurrences. An earlier detection may, in addition, lead to an increased rate of effective salvage interventions. However, associated outcome remains unknown. The usefulness of follow-up in terms of improving survival is limited for early salvage surgery after (failing) definitive CRT [3]. It would be of great interest to study the influence of the different methods of follow-up on the rate of detection of LRR, and the chances of performing salvage treatment. Particularly in the current era of enhanced surgical procedures in the salvage setting for EC, e.g. endoscopic resections [41], robot-assisted minimally invasive esophagectomy [42], and the advantages of high volume expertise centers [43,44].

In the Netherlands, follow-up ends five years post treatment. Duration of follow-up is not clearly specified in ESMO guidelines, whereas NCCN recommends annual follow-up even after five years. The current study demonstrated that most failures were developed within the first three years after CRT. After that point, surveillance for second primary tumors may be of importance, considering the high occurrence of a second SCC due to the close association of alcohol consumption and smoking habits [45]. Whether early detection and treatment of second primaries improves patient outcomes is currently unknown. Considering the impact of prolonged follow-up might have on patients quality of life and health care costs, we would propose to restrict follow-up to three years following CR after definitive CRT for proximal EC. Unless other factors regarding patients recovery, e.g. repeated dilatations, dietary or psychosocial needs, require continued surveillance. Furthermore, follow-up should be patient tailored in order to warrant patients' preferences.

The strength of our study is that we included a large cohort of patients in this rare disease, with long-term follow-up. The retrospective design of this study is however also inherent with some limitations. Details on applied RT techniques, time to response, subsequent recurrences were not collected. Furthermore, the number of patients with recurrences did not allow us to study independent predictive and prognostic factors for risk of LRR and radiation dose effect on treatment response. In addition, recurrence treatment outcomes should be considered with care, given the low patient numbers.

In conclusion, patients with a complete response after definitive CRT for proximal EC demonstrated high rates of infield LRR, suggesting methods to optimize locoregional control are necessary. Salvage treatment of isolated LRR resulted in favorable outcome. Hence, screening for LRR should be optimized. Furthermore, since nearly all recurrences occurred within three years after initial treatment, routine follow-up could be restricted.

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Data statement

The data that support the findings of this study are available from the corresponding author upon request.

CRediT authorship contribution statement

J. de Vos-Geelen: Conceptualization, Methodology, Software, Validation, Investigation, Writing - original draft, Project administration. **S.M.E. Geurts:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - review & editing. **G.A.P. Nieuwenhuijzen:** Conceptualization, Resources, Writing - review & editing. **F.E.M. Voncken:** Resources, Writing - review & editing. **J.A. Bogers:** Resources, Writing - review & editing. **P.M. Braam:** Resources, Writing - review & editing. **C.T. Muijs:** Resources, Writing - review & editing. **M.A. de Jong:** Resources, Writing - review & editing. **N. Kasperts:** Resources, Writing - review & editing. **T. Rozema:** Resources, Writing - review & editing. **G.J. Blom:** Resources, Writing - review & editing. **S.A.W. Bouwense:** Writing - review & editing, Visualization, Writing - review & editing. **L.B.J. Valkenburg-van Iersel:** Resources, Writing - review & editing. **P.M. Jeene:** Resources, Writing - review & editing. **F.J.P. Hoebers:** Conceptualization, Methodology, Writing - review & editing, Supervision. **V.C.G. Tjan-Heijnen:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

JV has served as a consultant for AstraZeneca, MSD, Pierre Fabre, and Servier, and has received institutional research funding from Servier. All outside the submitted work.

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CM had research collaborations with IBA, Siemens, Raystation, and Mirada. All outside the submitted work.

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The other authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.02.001.

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