BJR

Received: 15 April 2022 | Revised: 07 November 2022 | Accepted: 08 December 2022 | Published online: 12 January 2023

https://doi.org/10.1259/bjr.20220413

Cite this article as:
Chufal KS, Ahmad I, Bajpai R, Miller AA, Chowdhary RL, Makker J, et al. Tri-modality therapy in advanced esophageal carcinoma: long-term results and insights from a developing world, institutional cohort. *Br J Radiol* (2023) 10.1259/bjr.20220413.

FULL PAPER

Tri-modality therapy in advanced esophageal carcinoma: long-term results and insights from a developing world, institutional cohort

[1]KUNDAN SINGH CHUFAL, MD, [1]IRFAN AHMAD, DNB, [2]RAM BAJPAI, PhD, [3]ALEXIS ANDREW MILLER, FRANZCR, [1]RAHUL LAL CHOWDHARY, MD, [4,5]JASBIR MAKKER, MD, [6]ULLAS BATRA, MD, [7]SHRINIDHI NATHANY, MD, [1]MUHAMMED ISMAIL SHARIEF, DNB, [1]PREETHA UMESH, DNB, [2]MANSI SHARMA, MD, [2]PATEL AMRITH, MD, [1]ANJALI KAKRIA PAHUJA, MD, [1]JASKARAN SETHI, MD, [1]VARGHESE ANTONY, DNB and [1]MUNISH GAIROLA, MD, DNB

[1]Department of Radiation Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India
[2]Centre for Prognosis Research, School of Medicine, Keele University, Staffordshire, United Kingdom
[3]Department of Radiation Oncology, Illawara Cancer Care Center, Wollongong, New South Wales, Australia
[4]Neurogastroenterology and Gastrointestinal Motility Lab, BronxCare Health System, New York, United States
[5]Mt Sinai ICAHN school of Medicine, New York, United States
[6]Department of Medical Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India
[7]Department of Molecular Diagnostics, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India

Address correspondence to: Dr Irfan Ahmad
E-mail: *irfan.a@icloud.com*

Objective: To evaluate treatment outcomes in patients from a low-middle income country (LMIC) with esophageal carcinoma who underwent esophagectomy after neoadjuvant chemoradiation (NACRT/S).

Methods: Between 2010 and 2020, 254 patients (median follow-up: 53 months) met our inclusion criteria. Out-of-field nodal regions were determined by reviewing individual radiotherapy plans. Cox regression modelling was performed to analyze overall survival (OS) and recurrence-free survival (RFS), while pathological complete response (pCR) prediction utilized Poisson regression.

Results: The median OS was 71.4 months (interquartile range: 19.6–∞), RFS did not reach the median and pCR rate was 46%. On multivariable Cox regression, BMI [0.93 (0.89–0.98); 0.94 (0.89–0.99)] and absence of out-of-field node with extranodal extension (ENE)[0.22 (0.09–0.53); 0.30 (0.12–0.75)] influenced OS and RFS, respectively. Age [1.03 (1.01–1.06)], nodal stage [cN2-3 *vs* cN0: 2.67 (1.08–6.57)] and adventitial involvement [2.54 (1.36–4.72)] also influenced OS, while involved margins [3.12 (1.24–7.81)] influenced RFS. On multivariable Poisson regression, non-CROSS-chemotherapy regimens [0.65 (0.44–0.95)] and residual primary disease on pre-surgical imaging [0.73 (0.57–0.93)] were significantly associated with pCR. The most frequently involved in-field and out-of-field nodal regions were the periesophageal and perigastric (greater and lesser curvature) regions, respectively.

Conclusion: NACRT/S is feasible and effective in patients from LMIC. Out-of-field ENE merits further investigation as a prognostic factor since it significantly influenced both OS and RFS.

Advances in knowledge: The results of clinical trials are replicable in LMICs. Out-of-field ENE is an independent prognostic factor for OS and RFS.

INTRODUCTION

Remarkable progress has taken place in improving the prognosis of locally advanced esophageal carcinoma, with neoadjuvant chemoradiation followed by surgery (NACRT/S) emerging as the standard of care for medically fit patients.[1–3] Minimally invasive surgical techniques, improvements in supportive care during and after neoadjuvant treatment, and refinements in radiotherapy techniques have contributed to establishing this treatment paradigm.[4,5] However, the global burden associated with esophageal cancer is unequally distributed. Up to half of all cases diagnosed worldwide are in low-middle income countries (LMICs) of the Asian esophageal cancer belt and projections suggest a further 50% increase in the next decade, but resources remain limited.[6]

Access and affordability remain the key concerns in LMICs, and consequently patients often present late in the course of disease.[7] While the epidemiological shift in high income countries from squamous cell carcinoma (SqCC) to adenocarcinoma (AdenoCa) prompted clinical trials being designed for esophageal AdenoCa, the predominant histology in LMICs remains SqCC.[8] Whether the worldwide standards of care apply to patients from LMICs remains an open question, as the literature is sparse.[9] The egalitarian answer to this question would be to increase representation from LMICs in multinational clinical trials, while the pragmatic answer would be to conduct context-specific research that addresses problems relevant to the region.[7]

Towards that end, our primary objective was to evaluate the long-term outcomes and pathologic response predictors in patients from a LMIC with locally advanced, operable esophageal carcinoma who underwent NACRT/S.

METHODS AND MATERIALS

Patient population

We retrieved all patients who underwent esophagectomy between January 2010 and December 2020 from our institutional cancer registry (NCT04489368; RGCIRC/IRB/80/2020) and included for analysis: (a) pathologically proven *de novo* SqCC/AdenoCa of the thoracic esophagus [excluding gastro-esophageal junction (GEJxn) tumors] who received NACRT/S, and; (b) all oncological interventions (radiotherapy, chemotherapy, and surgery) delivered at our institution (Rajiv Gandhi Cancer Institute & Research Centre, New Delhi) after multidisciplinary meeting discussion.

Pre-treatment evaluation included history, physical examination, hematological and biochemical investigations, UGI endoscopy (UGIE), and imaging studies [either whole body ^{18}fludeoxyglucose positron emission tomography CT (^{18}FDG PET-CT) or high-resolution chest CT (HRCT)]. Medical records, radiological investigations, and details of each oncological intervention were reviewed. All pre-2018 patients were clinically and pathologically restaged according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system and retrospectively classified as CROSS-Eligible/Ineligible based on CROSS-trial criteria.[1,10] Surveillance imaging [either ^{18}FDG PET-CT or HRCT (with CT abdomen and pelvis)] was performed at the treating oncologist's discretion (every 3–6 months) with UGIE initiated on symptoms and/or suspicious imaging findings. Due to the ongoing COVID-19 pandemic, outcome data were gathered by telephonic/video consultation with the patient or relatives (For additional details, please see Supplementary Material 1). The data set was frozen for analysis on June 15, 2021.

The primary end points were overall survival (OS), recurrence-free survival (RFS) (calculated from treatment start date), and pathological response to NACRT.

Treatment details

All patients were treated on a 6MV linear accelerator after planning conventional or conformal techniques [3-dimensional conformal radiotherapy technique (3DCRT), intensity modulated radiotherapy technique (IMRT), or volumetric modulated arc therapy (VMAT)]. Prior to the publication of the long-term results of the CROSS-trial, both conventional and conformal radiotherapy used two phases (with a minority receiving boost to primary as a third phase). Elective nodal irradiation (ENI) was not performed. After the CROSS-trial publication, our doses and target volumes gradually matched the CROSS-protocol (n = 124), and patients were subsequently treated using a single phase with IMRT or VMAT (For additional details, please see Supplementary Material 1).[11] For statistical modelling, the dose was converted to equivalent dose in 2 Gy using an α/β value of 10 [EQD_{2Gy} (α/β = 10)].[12] Chemotherapy prescribing after the CROSS-publication followed a similar change as 124 patients received weekly concurrent Paclitaxel (50 mg/m^2) and Carboplatin (AUC2). Prior to 2015, the most commonly delivered chemotherapy was weekly Cisplatin (35 mg/m^2) (n = 87) or infrequently, weekly Cisplatin (25 mg/m^2) and 5-Fluorouracil (500 mg/m^2) (n = 22).

Almost all patients underwent imaging (HRCT or ^{18}FDG PET-CT) before surgical resection, and only metastatic progression influenced the decision to proceed with esophagectomy. Response was measured using RECIST 1.1 (HRCT) or PERCIST (^{18}FDG PET-CT) criteria.[13,14] Most patients underwent surgery within 8 weeks post-NACRT completion and underwent a Mckeown's or Ivor-Lewis esophagectomy, either by open (transhiatal/thoracotomy) (n = 107) or minimally invasive [± robotic assistance (daVinci Si robotic system)] (n = 137) approach with two-field lymph node dissection. Ten patients were converted from minimally invasive to open approach. Complications were retrospectively classified using the Esophageal Complications Consensus Group definitions.[15]

Pathological evaluation and location of nodal regions in relation to radiotherapy fields

Pathological evaluation followed the College of American Pathologists (CAP) guidelines for esophageal cancer reporting.[16] The pathological data prior to 2013 were re-evaluated to conform to this standard, and tumor regression grading used the CAP system.

Surgically labeled and unlabeled lymph node regions were classified according to the radiotherapy plan (3DCRT/IMRT/VMAT) with a pathologist and by correlation with the IASLC mediastinal nodal contouring atlas and consensus esophageal contouring atlas.[17,18] Regions outside the 50% isodose were deemed 'out-of-field'. For patients treated with conventional technique, the digitally reconstructed radiograph (DRR) of pre-treatment HRCT/^{18}FDG PET-CT was registered with the 2D-simulator films, and regions more than 1 cm outside the field borders were considered 'out-of-field'. Since the RT field/target volume design included all known gross disease at primary and nodal sites, 'out-of-field' nodes in our analysis represent occult pathological nodal positivity rather than a 'geographic miss'.

The median number of nodes resected per patient was 17 (IQR: 12–22), distributed equally within in-field [median (IQR): 8 (4–13)] and out-of-field [median (IQR): 8 (3–13)] nodal regions. The overall nodal positivity rate was 3.2% (144/4466 nodes), while the nodal positivity rate in patients who harbored residual nodal disease was 13.1% (144/1097 nodes). We defined sampling frequency (SF) of nodal regions as: number of patients with ≥1 dissected node from that region stratified by primary location/ total number of patients stratified by primary location.

Statistical methods—clinical outcomes

Descriptive statistics were used for baseline patient characteristics and reported as median with interquartile range (IQR) (continuous variables) or frequencies and percentages (categorical variables).

In survival analyses, the event of interest was all-cause mortality (OS) and disease recurrence (RFS). Median survival time (months) was estimated using the non-parametric Kaplan–Meier (KM) method, and Cox-regression analytical model was applied to explore significant factors associated with OS and RFS, with results presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Departure from the proportional hazard assumption was assessed with Schoenfeld's residual and graphical inspection of log-log plots, and all the predictor variables satisfied the criterion of being asymptotic.[19]

Prevalence ratios (PR) were calculated for complete response rather than odds ratios to prevent overestimation in measuring the strength of association.[20] PR indicates the magnitude of the prevalence of an outcome in one group of individuals with characteristics relative to the group without the characteristics. A Poisson regression using a generalized linear model with robust variance based on Huber's sandwich estimator was performed to examine the association between complete response and clinical characteristics, with results presented as PR with 95% CI.[21]

Uni- and multi-variable regression models were fitted to explore the strength of the association. We selected variables for the multivariable modelling if any covariate had a p-value < 0.1 in the univariable model. To ensure the validity of the results, we checked collinearity (where variance inflation factor >10) between covariates in the model and checked clinically meaningful interactions by including cross-product terms (considered significant if $p < 0.1$). A two-sided p-value of <0.05 was considered statistically significant.

We addressed selection bias using the restriction method, where records of all patients with esophageal cancer were screened, and those meeting our inclusion criteria were analyzed (For additional details, please see Supplementary Material 1). This report was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines.[22] Statistical analysis was carried out using Stata software v. 17.0 (StataCorp, College Station, TX) and Prism version 9 (Graphpad Software, San Diego, CA).

RESULTS

A total of 254 patients with a median follow-up of 53 months (IQR: 21.7–78.3) were analyzed, being predominantly males (57%) with SqCC (94%) located in the middle or lower esophagus (85%) and AJCC cT_{3-4} (97%) or cN_{0-1} (78%) disease (Table 1). Most patients received at least five cycles of concurrent chemotherapy and completed their prescribed course of radiotherapy without any delays (Table 2). Open esophagectomy was the most

Table 1. Baseline characteristics

	n	%
Median age—years (IQR)	55 (48–62)	-
Gender (Male/Female)	145/109	57% / 43%
Smoking status		
Current or Former smoker	152	60%
Never smoker	102	40%
Median BMI—Kg/m^2 (IQR)	23 (20–26)	-
BMI category		
Underweight/Normal	33/91	13 % / 36%
Overweight/Obese	41/89	16 % / 35%
Histology		
SqCC	239	94%
AdenoCa	15	6%
Location of primary		
Upper 1/3rd	37	14.6%
Middle 1/3rd	103	40.6%
Lower 1/3rd	114	44.9%
Lower 1/3rd extending to GEJxn (n = 114)	37	32%
AJCC clinical T stage (eighth Ed)		
cT_{1-2}	7	3%
cT_3	205	81%
cT_4	42	16%
AJCC clinical N stage (eighth Ed)		
cN_0	93	37%
cN_1	104	41%
cN_2	34	13%
cN_2	23	9%
Median CCL of primary—cm (IQR)	5.1 (4–6.7)	–
Post hoc assessment of CROSS-eligibility[1]		
Eligible	157	62%
Ineligible	97	38%
cT_4 / cN_{2-3}/CCL > 8 cm (n = 77)	28/41/8	29 % / 42 % / 8%
cT_4 and/or cN_{2-3} and/or CCL >8 cm	20	21%
Median time from initial presentation to treatment - days (IQR)	7 (4–11)	–

AJCC, American Joint Committee on Cancer;AdenoCa, Adenocarcinoma; BMI, Body Mass Index; CCL, Craniocaudal Length; Ed, Edition; GEJxn, Gastro-oesophageal Junction; IQR, Interquartile Range; SqCC, Squamous Cell Carcinoma.

Table 2. Details of neoadjuvant chemoradiation

	n	%
Radiotherapy		
RT technique		
Conventional or 3DCRT	139	55%
IMRT or VMAT	115	45%
Planned RT phases		
Single	104	41%
Two	142	56%
Three	8	3%
Median RT dose—Gy (Range)		
Single phase	41.4 (40–50.4)	–
Two phases	50.4 (43.2–63.4)	–
Three phases	50.4 (47.4–65.6)	–
RT completion		
Without any delay	135	53%
Delayed (≥1 day)	119	47%
Median delay–days (IQR)	2 (1–3)	–
RT completion		
Without any delay—Conventional or 3DCRT	67	48%
- IMRT or VMAT	68	59%
Median time between RT completion and surgery—days (IQR)	55 (49–62)	–
RT Technique—Conventional or 3DCRT	55 (49–61)	–
- IMRT or VMAT	56 (50–64)	–
RT phase—Single	55 (50–63)	–
- Two	55 (48–62)	–
- Three	58 (54–91)	
Chemotherapy		
Concurrent chemotherapy regimen		
Cisplatin alone	87	34%
Paclitaxel+Carboplatin	124	49%
Cisplatin+5-Flourouracil	22	9%
Others	21	8%
Median no. of delivered chemotherapy cycles (IQR)		
Cisplatin alone	5 (4–5)	–
Paclitaxel+Carboplatin	5 (4–5)	–
Cisplatin+5-Flourouracil	5 (4–5)	–
Post-NACRT HRCT/PET-CT performed before surgery	245	96%
Complete response on imaging	79	32%
Partial response or stable disease on imaging	166	68%
Median time of imaging evaluation Post-NACRT completion—days (IQR)	42 (38–47)	–

(Continued)

Table 2. (Continued)

3DCRT, 3-Dimenional Conformal Radiotherapy Technique; Gy, Gray; HRCT, High Resolution Computed Tomography; IMRT, Intensity Modulated Radiotherapy Technique; IQR, Interquartile range; PET-CT, Positron Emission Tomography CT; RT, Radiotherapy; VMAT, Volumetric Modulated Arc Therapy.

common surgical approach until 2014, following the introduction of minimally invasive esophagectomy in 2011 (Table 3), without any statistical difference in procedure-related metrics (mortality, complications, margin positivity, lymph nodal yield, and time to discharge) between both approaches (Table 3).

Complete response rate on pre-surgical imaging was 32% (Table 2), while actual pCR rate was 46% (Table 3). Pathological residual disease (pRD)(n = 138, SqCC *vs* AdenoCa = 125 *vs* 13) was common at the primary site only [ypT+N0, n = 75 (54%)]. Those with pRD at nodal sites (n = 63, SqCC *vs* AdenoCa = 57 *vs* 6) (total nodes involved = 144, SqCC *vs* AdenoCa = 129 *vs* 15) frequently harbored disease in out-of-field nodal regions [n = 37 (59%); 87/144 involved nodes] with extranodal extension (ENE) [n = 36 (57%); 84/144 involved nodes]. Other adverse features found in patients with pRD were involvement of adventitia (43%), lymphovascular invasion (27%), and perineural invasion (13%) (Table 3).

Overall survival and recurrence-free survival

The cohort's median OS was 71.4 months (IQR: 19.6–∞), with a median RFS which was not reached (Figure 1). The median OS and RFS was not reached for patients with pCR, while it was 29.5 months (95% CI: 17.0–42.0) and 22.7 months (95% CI: 6.9–38.5) respectively, for patients with pRD. Factors associated (p < 0.1) with OS and RFS on univariable analysis (Supplementary Material 1) underwent multivariable Cox Proportional Hazards modelling (Figure 2). Increasing age [HR: 1.03 (1.01–1.06), p = 0.015], higher nodal stage [cN_{2-3} *vs* cN_0; HR: 2.67 (1.08–6.57), p = 0.033] and adventitia involvement [HR: 2.54 (1.36–4.72), p = 0.003] were associated with worse OS, while higher BMI [HR: 0.93 (0.89–0.98), p = 0.011] and absence of out-of-field node with ENE [HR: 0.22 (0.09–0.53), p = 0.001] were associated with improved OS. Residual primary disease on pre-surgical imaging was associated with worse OS [HR: 1.56 (0.94–2.59), p = 0.087], with the results approaching statistical significance.

Involved surgical margins [HR: 3.12 (1.24–7.81), p = 0.015] was associated with worse RFS, while higher BMI [HR: 0.94 (0.89–0.99), p = 0.044] and absence of out-of-field node with ENE [HR: 0.30 (0.12–0.75), p = 0.009] were associated with improved RFS. Increasing age [HR: 1.02 (1.00–1.05), p = 0.067], higher nodal

Table 3. Surgical treatment details and results of histopathological analysis

	n	%
Surgery		
Surgical technique		
Open approach	107	42%
Minimally invasive approach	137	54%
Minimally invasive converted to open approach	10	4%
ECCG surgical complications (Overall)—Grade 2 or higher	32	13%
Open approach[a]	17	14%
Minimally invasive approach	15	11%
Mortality rate		
Open approach[a] (30 day/90 day)	6/2	5%/2%
Minimally invasive approach (30 day/90 day)	8/2	6%/1.5%
Margin positivity rate		
Open approach[a]	2	1.7%
Minimally invasive approach	5	3.6%
Median time to discharge–days (IQR)		
Open approach[a]	11 (10–14)	–
Minimally invasive approach	10 (9–12)	–
Median no. of total dissected nodes per patient - (IQR)		
Open approach[a]	16 (12–21)	–
Minimally invasive approach	17 (12–23)	–
Pathology		
Response to NACRT		–
Complete pathologic response (pCR)	116	46%
Partial response (pRD)	138	54%
Disease at primary site only (ypT_{any} ypN_0)	75	54%
Disease at primary and nodal site (ypT_{any} ypN_{any})	49	36%
Disease at nodal site only (ypT_0 ypN_{any})	14	10%
Median no. of residual nodes ($ypT_{0\ or\ Any}$ ypN_{any})(*n* = 63) - IQR	1 (1–3)	–
Residual nodes with extranodal extension	36	57%
Adverse pathological features in patients with pRD		
Lymphovascular invasion	37	27%
Perineural invasion	18	13%
Involvement of adventitia	60	43%
Involvement of GEJxn in Lower 1/3rd (*n* = 114)	9	8%

GEJxn, Gastro-oesophageal Junction; IQR, Interquartile range;pRD, pathological residual disease.
[a]Patients converted from minimally invasive to open approach were counted as open.

stage [cN_{2-3} *vs* cN_0; HR: 2.22 (0.87–5.67), $p = 0.095$] [cN_1 *vs* cN_0; HR: 1.76 (0.98–3.16), $p = 0.060$] and involvement of adventitia [HR: 1.86 (0.97–3.58), $p = 0.063$] were also associated with worse RFS, with the results approaching statistical significance.

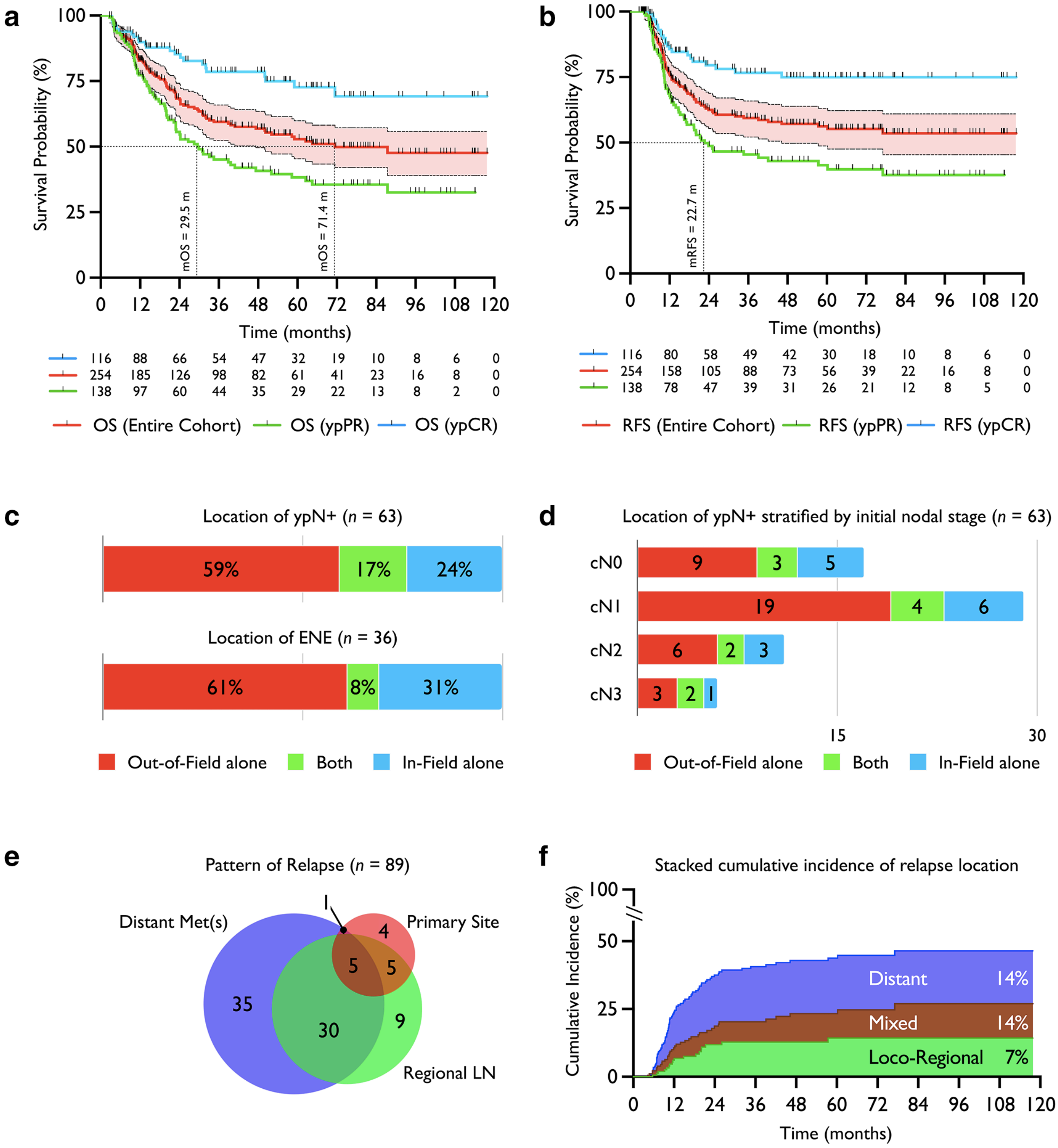
Pathological response to neoadjuvant chemoradiation

On univariable Poisson regression (Supplementary Material 1), pre-surgical factors which were associated with pCR at primary site, nodal regions and overall complete response ($p < 0.1$) were selected for multivariable modelling (Figure 3). Non-CROSS-protocol chemotherapy regimens [PR: 0.63 (0.45–0.87), $p = 0.005$] and residual disease at primary site on pre-surgical imaging [PR: 0.67 (0.53–0.84), $p = 0.001$] were significantly associated with pRD at primary site, while increasing craniocaudal length [PR: 0.94 (0.88–1.00), $p = 0.056$] approached significance.

Variables significantly associated with pCR at nodal site were female gender [PR: 1.17 (1.03–1.34), $p = 0.019$] and AJCC cT_4 stage [PR: 1.31 (1.17–1.47), $p < 0.001$], while residual disease at nodal site on pre-surgical imaging [PR: 0.84 (0.71–1.02), $p = 0.080$] approached significance.

Non-CROSS-protocol chemotherapy regimens [PR: 0.65 (0.44–0.95), $p = 0.026$] and residual disease at primary site on pre-surgical imaging [PR: 0.73 (0.57–0.93), $p = 0.013$] were significantly associated with overall pathologic residual disease, while increasing craniocaudal length [PR: 0.93 (0.87–1.01), $p = 0.073$], modern RT techniques [PR: 1.29 (0.97–1.73), $p = 0.084$] and female gender [PR: 1.25 (0.96–1.61), $p = 0.094$] approached significance.

Figure 1. Treatment outcomes of the study cohort. Kaplan–Meier plots for: (a) OS, and (b) RFS. Both plots include the OS and RFS for the entire cohort (with shaded 95% confidence interval) and are further stratified by pathological response to NACRT. (c) Overall pattern of residual nodal disease detected after NACRT in relation to RT fields. (d) Pattern of residual nodal disease detected after NACRT in relation to RT field, further stratified by Pre-NACRT clinical nodal stage. (e) Pattern of relapse in the overall cohort. (f) Stacked cumulative incidence of relapse patterns in the entire cohort. *Abbreviations*: cN, Clinical N stage (AJCC eighth Edition); ENE, extranodal extension; LN, lymph nodes; mOS, median overall survival; mRFS, median recurrence free survival; ypCR, post-neoadjuvant pathological complete response; ypN+, post-neoadjuvant residual node detected; ypPR, post-neoadjuvant pathological partial response.

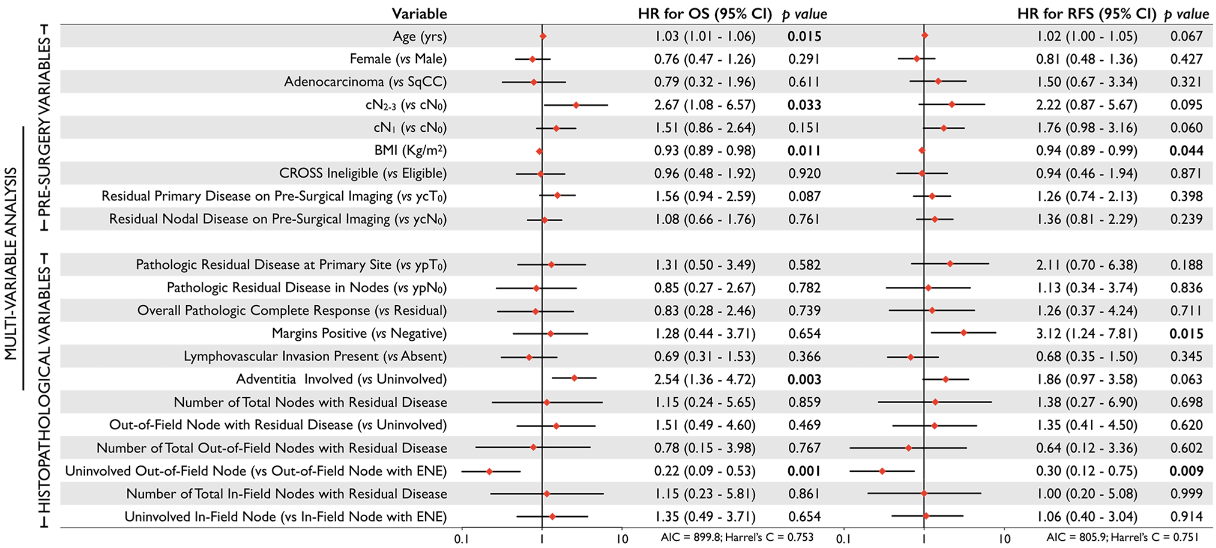


Distribution of nodes with pathologic residual disease

Residual nodal disease remained in 63 patients (upper esophagus, n = 5; middle esophagus, n = 32; lower esophagus, n = 26) (Figure 4) most of which were found out-of-field exclusively (n = 37) and in patients with pre-NACRT node positive disease (n = 46).

Periesophageal nodes were the most frequently sampled in-field region (SF: 80–92%) with a nodal positivity rate of 7.7% (1/13 nodes), 15.5% (23/148 nodes), and 10.1% (14/138 nodes) for upper, middle and lower esophageal primaries, respectively. The second highest in-field sampling frequency was observed in the subcarinal nodal region (SF: 40–53%) with a nodal positivity rate

Figure 2. Multivariable Cox proportional hazards model for OS and RFS. *Abbreviations*: AIC, Akaike's Information Criterion; BMI, body mass index; CI, confidence interval; cN, clinical N stage (AJCC eighth Edition); ENE, extranodal extension; HR, hazard ratio; SqCC, squamous cell carcinoma; ycN_0, post-neoadjuvant clinical complete response at nodal sites; ycT_0, post-neoadjuvant clinical complete response at primary site; ypN_0, post-neoadjuvant pathological complete response in nodes; ycT_0, post-neoadjuvant pathological complete response at primary site.



of 25% (1/4 nodes), 7.8% (4/51 nodes), and 15.4% (6/39 nodes) for upper, middle and lower esophageal primaries, respectively.

The highest out-of-field sampling frequency was observed in the greater and lesser curvature nodal regions (SF, greater curvature: 75–81%; SF, lesser curvature: 58–80%). The nodal positivity rate in the greater curvature nodal region was 2.8% (1/36 nodes), 10.4% (15/144 nodes), and 13.7% (20/146 nodes) for upper, middle, and lower esophageal primaries, respectively, while the corresponding rate in the lesser curvature nodal region was 20% (2/10 nodes), 19.4% (26/134) and 18.3% (19/104).

DISCUSSION

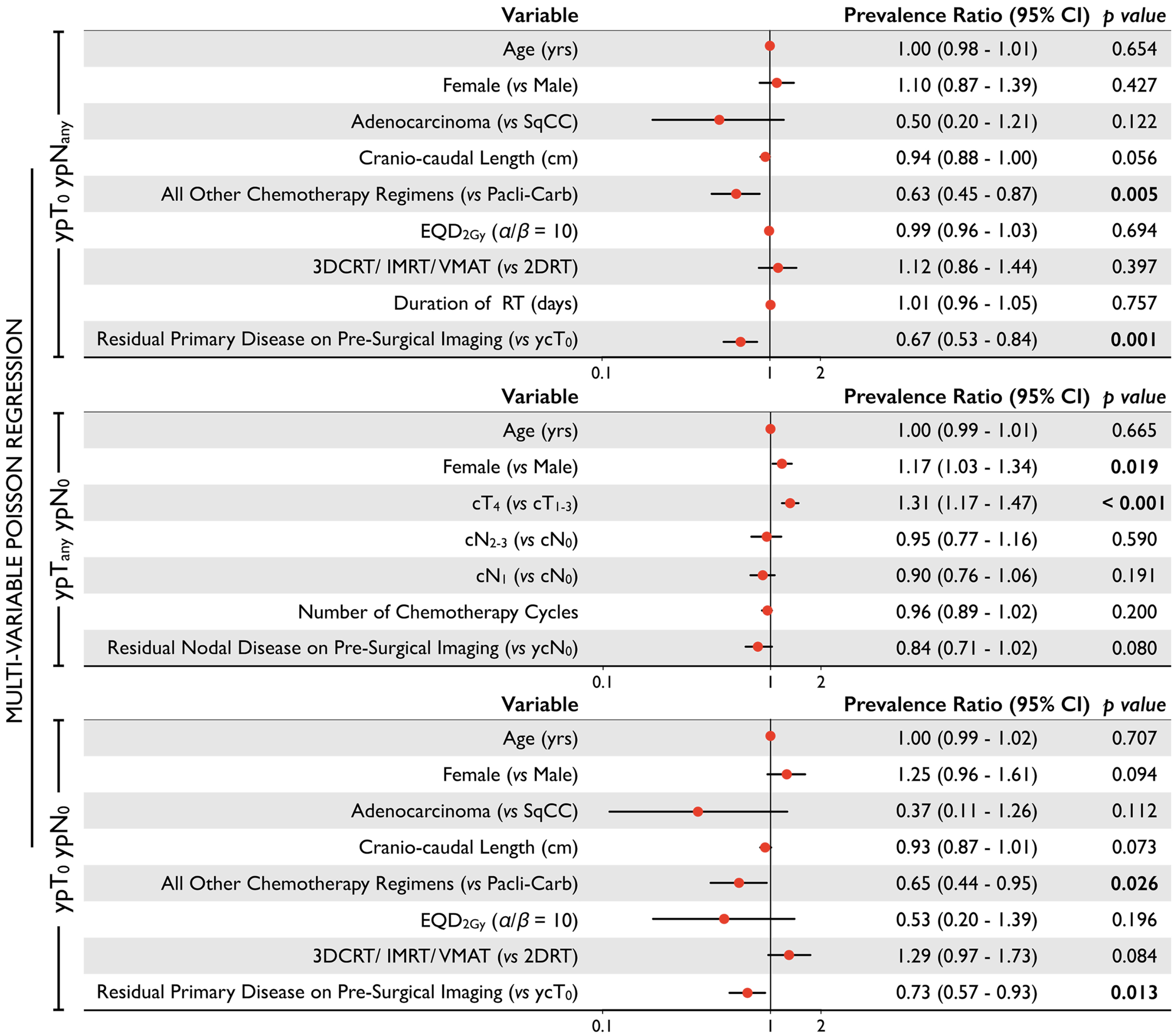
Over the last decade, NACRT/S has become the standard of care for medically operable, locally advanced esophageal cancer. With the recent Checkmate 577 trial reporting a benefit with PD1 inhibitors in patients with pRD, outcomes may improve further.[23] It is worth highlighting the parallel evolution of NACRT/S for AdenoCa/SqCC in the west, while in Japan the preferred approach for SqCC remains NACT/S.[24] Though the Japanese trials demonstrated the benefit of NACT over adjuvant chemotherapy, trials conducted elsewhere could not demonstrate similar efficacy, and results of perioperative chemotherapy were underwhelming.[24] Subsequently, the CROSS (predominantly AdenoCa) and $NEOCRTEC_{50}10$ (SqCC) trials established NACRT/S as the worldwide standard, except in Japan.[1–3,11,25–30] This reservation in adoption stems from the lack of benefit with additional RT to NACT in the NeoRes trial (predominantly AdenoCa) and the preliminary results of the JCOG1109 (SqCC) demonstrating equivalence between NACT/S and NACRT/S.[31,32] Ongoing trials exploring the optimal NACRT regimen (NCT02359968), omission of surgery in complete clinical responders to NACRT (NCT04886635, NCT02551458) and integration of immunotherapy with NACRT (NCT02998268, NCT04807673, NCT03544736, NCT04568200, NCT04848753, NCT03957590) will further influence management paradigms.[33]

Applying results from these clinical trials to patients from the developing world is not straightforward, as indigenous trials are rarely designed to assess efficacy.[7] Furthermore, strict inclusion criteria often exclude up to half of the total screened patients leading to limited participation from the developing world, if permitted at all.[34] Therefore, institutional analyses offer the highest quality of evidence in LMICs, and our real-world NACRT/S experience in predominantly SqCC reassuringly demonstrates comparable efficacy (Figure 5). Similar variables influencing OS and RFS have been reported elsewhere and validated in a comprehensive meta-analysis of prognostic factors.[35]

We add to the growing literature highlighting residual nodal disease after NACRT/S as a significant prognostic factor affecting outcomes and reinforce the aforementioned trials' conclusion that de-emphasizes the importance of the number of nodes dissected.[36,37] Similar to our results, investigators have identified ENE as a strong prognostic factor influencing outcomes, and two meta-analyses of observational studies also demonstrate its significance irrespective of histology or neoadjuvant treatment (NACT or NACRT).[38,39] Consequently, there is increasing support to include ENE in the AJCC staging criteria.[40]

While no randomized trial has addressed residual nodal disease specifically, an analysis of NCDB patients suggests improved outcomes with adjuvant chemotherapy.[41] In the recent CheckMate 577 trial, more than half of all patients harbored residual nodal disease ($\geq ypN_1$) and advanced residual primary disease ($ypT_{3/4}$), yet DFS was improved only in patients with residual nodal disease [HR for DFS: $\geq ypN_1$, 0.67 (0.53–0.86); $ypT_{3/4}$, 0.84 (0.64–1.11)].[23] In fact, patients with pCR at the primary site

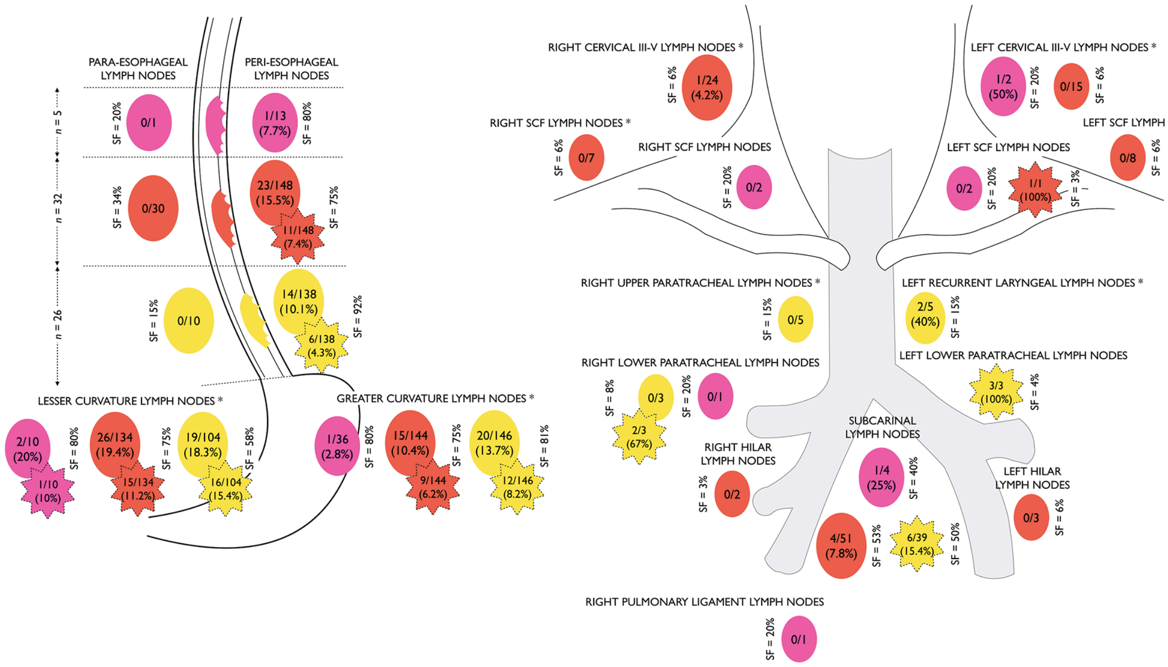
Figure 3. Multivariable Poisson regression model for prediction of pathological complete response at primary site (ycT_0 ycN_{any}), nodes (ycT_{any} ycN_0) and overall complete response (ycT_0 ycN_0). *Abbreviations*: 2DRT, two-dimensional radiotherapy technique; 3DCRT, three-dimensional conformal radiotherapy technique; cN, clinical nodal stage (AJCC eighth Edition); cT, clinical primary stage (AJCC eighth Edition); EQD_{2Gy} (α/β = 10), equivalent dose in 2 Gy using an α/β value of 10; IMRT, intensity modulated radiotherapy technique; Pacli-Carb, Paclitaxel and Carboplatin; RT, radiotherapy; SqCC, squamous cell carcinoma; VMAT, volumetric modulated arc therapy; ycN_0, post-neoadjuvant clinical complete response at nodal sites; ycT_0, post-neoadjuvant clinical complete response at primary site.



derived maximum benefit [ypT_0, HR for DFS: 0.35 (0.15–0.82)], implying that they harbored only residual nodal disease. Future trials should address the role of adjuvant systemic treatment (chemotherapy or immunotherapy) in patients with residual nodal disease (stratified by ENE) after NACRT/S.

From the radiation oncologists' perspective, understanding the location of residual nodal disease is vital to decide whether changes in treatment volumes are necessary for the next generation of clinical trials. The CROSS-investigators reported infrequent SCF and celiac axis recurrences, concluding that elective irradiation is unwarranted, but they did not analyze the topography of residual nodal disease.[2] Two Dutch (predominantly AdenoCa) analyses and one Japanese (SqCC) analysis have explored the topography of residual nodal disease and RT field coverage.[42–44] Out-of-field nodal positivity rates ranged from 8.5 to 33%, with the Japanese analysis reporting a 5-year OS and RFS of 0% (despite ENI). We report similar findings, though the high out-of-field nodal positivity rate can be attributed to our institutional policy of avoiding ENI and a significant proportion of patients receiving single-agent Cisplatin. Finally, our analysis demonstrates that out-of-field ENE may be an independent prognostic factor for

Figure 4. Distribution of residual nodes stratified by primary site, in-field/out-of-field status and ENE. Nodal regions marked with (*) were out-of-field. Values within star shape represent nodes with ENE. Values within oval shape represent nodes without ENE. *Abbreviations*: ENE, extranodal extension; SCF, supraclavicular fossa; SF, sampling frequency (for definition, please see text).



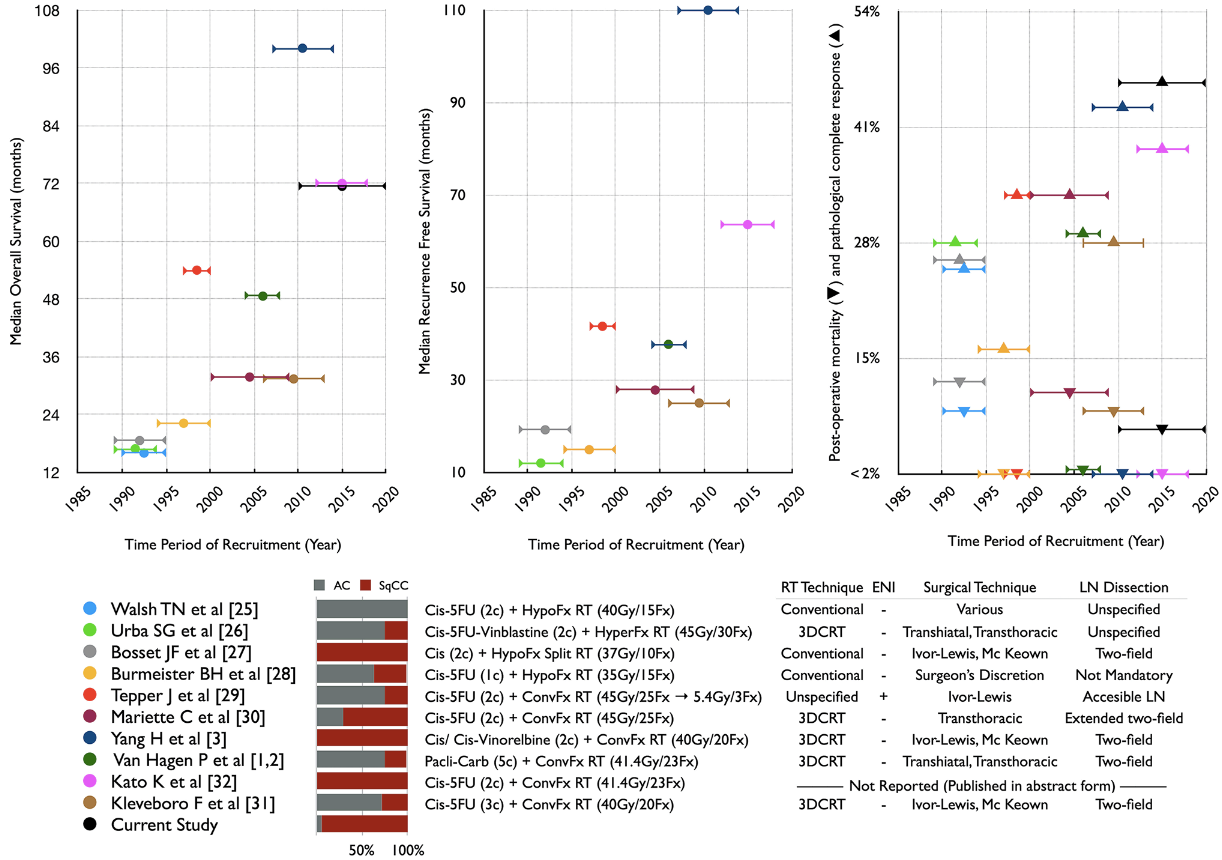
both OS and RFS, which has not been reported previously. In the near future, the TIGER study (NCT03222895) will provide more insight into the topographical importance of residual nodes.

While most variables influencing pCR in our analysis have been previously reported, our data demonstrate the inability of non-CROSS-chemotherapy regimens to induce pCR.[45–47] This may reflect our previous selective use of weekly Cisplatin rather than the Cisplatin-5FU protocol for frail patients. Rather than a weakness of our analysis, the implications of these real-world decisions are meaningful to the practicing oncologist because clinical trials are designed to demonstrate effectiveness in relatively healthier patients.

The retrospective nature of our analysis is its main limitation, though we minimized selection bias by restricting our analysis to pre-specified selection criteria. The perceived limitation of being an institutional analysis actually facilitated complete capture of variables from treatment records and permitted an in-depth analysis, though a multi-institutional collaborative analysis would be ideal. Despite our analysis representing the largest experience with NACRT/S from our country, it is still modest considering the magnitude of yearly incident cases. The most important contributing factor to the final sample size was the cost associated with NACRT/S and while the clinical characteristics of our patients are comparable to other analyses from LMICs, the demographic profile was composed of a higher socioeconomic stratum. Consequently, it is plausible that a more socioeconomically diverse data set could yield effect sizes which may differ from our analysis. Finally, the lack of detailed toxicity data is a weakness of our analysis which cannot be overcome due to variable entry of toxicity data in treatment records (a consequence of data extracted over a decade).

In conclusion, our long-term results demonstrate the efficacy and feasibility of NACRT/S for esophageal cancer in LMICs and when undertaken, the combination of Paclitaxel with Carboplatin results in higher probability of achieving a pCR. The presence of extranodal extension after esophagectomy (especially when found in nodal regions which were not irradiated) portends a poor prognosis and warrants inclusion in future iterations of our staging systems.

Figure 5. Graphical summary of outcomes from clinical trials which investigated NACRT and surgery, over the last three decades. Horizontal bars represent the years during which recruitment took place in respective trials and only median values for overall survival and RFS are plotted (without confidence intervals). Note: Since the RFS of our study population did not reach the median, it is not depicted on the RFS plot. *Abbreviations*: Cis, Cisplatin; Cis-5FU, Cisplatin with 5-Flourouracil; ConvFx, conventional fractionated; ENI, elective nodal irradiation; Fx, fractions; Gy, gray; HyperFx, hyperfractionated; HypoFx, hypofractionated; NR, not reported; Pacli-Carb, Paclitaxel and Carboplatin; RFS, recurrence-free survival; RT, radiotherapy.



CONTRIBUTORS

All authors contributed equally in the design, conception, analysis and writing of this manuscript.

DATA AVAILABILITY STATEMENT

This study was based on institutional cancer registry data. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form). Reasonable requests for access to data will be considered on an individual basis, by contacting the corresponding author.

PRIOR PRESENTATIONS

The results of this analysis have been presented in abstract form at the annual ASTRO 2020 (virtual) and ESTRO 2021 (Madrid, Spain) meetings.

ETHICS APPROVAL

The authors state that they have obtained informed consent from the participants and that institutional ethics committee waived the requirement for IRB approval.

REFERENCES

1. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074–84. https://doi.org/10.1056/NEJMoa1112088
2. Oppedijk V, van der Gaast A, van Lanschot JJB, van Hagen P, van Os R, van Rij CM, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014; **32**: 385–91. https://doi.org/10.1200/JCO.2013.51.2186
3. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced esophageal squamous cell carcinoma: the neocrtec5010 randomized clinical trial. *JAMA Surg* 2021; **156**: 721: 721–29: . https://doi.org/10.1001/jamasurg.2021.2373

4. Straatman J, van der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial. *Ann Surg* 2017; **266**: 232–36. https://doi.org/10.1097/SLA.0000000000002171
5. Lin SH, Wang L, Myles B, Thall PF, Hofstetter WL, Swisher SG, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. *International Journal of Radiation Oncology*Biology*Physics* 2012; **84**: 1078–85. https://doi.org/10.1016/j.ijrobp.2012.02.015
6. Hull R, Mbele M, Makhafola T, Hicks C, Wang SM, Reis R, et al. A multinational review: oesophageal cancer in low to middle-income countries (review). *Oncol Lett* 2020. https://doi.org/10.3892/ol.2020.11902
7. Ranganathan P, Chinnaswamy G, Sengar M, Gadgil D, Thiagarajan S, Bhargava B, et al. The international collaboration for research methods development in oncology (credo) workshops: shaping the future of global oncology research. *Lancet Oncol* 2021; **22**: e369–76. https://doi.org/10.1016/S1470-2045(21)00077-2
8. Sekar A, Rajendra A, Noronha V, Mokal S, Patil VM, Menon N, et al. The epidemiological trend of esophageal cancer in mumbai, india over the past two decades. *JCO* 2021; **39**: e16095. https://doi.org/10.1200/JCO.2021.39.15_suppl.e16095
9. Rao T S, Raju KVVN, Patnaik SC, Reddy P, Saksena AR, Rajappa S, et al. Influence of neoadjuvant therapy on outcomes in patients with resectable carcinoma of esophagus and gastro-esophageal junction from a tertiary cancer care center in India. *J Surg Oncol* 2021; **123**: 1547–57. https://doi.org/10.1002/jso.26444
10. Rice TW, Kelsen D, Blackstone EH, et al. et alEsophagus and Esophagogastric Junction. In: Amin MB, Edge SB, Greene FL, et al., eds. AJCC Cancer Staging Manual. New York: Springer 2017. 185–202.
11. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090–98. https://doi.org/10.1016/S1470-2045(15)00040-6
12. Joiner MC, van der Kogel AJ. *Basic Clinical Radiobiology*. Fifth ed. CRC Press/Taylor & Francis Group; 2018., pp.112–24. https://doi.org/10.1201/9780429490606
13. Schwartz LH, Seymour L, Litière S, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-standardisation and disease-specific adaptations: perspectives from the RECIST working group. *Eur J Cancer* 2016; **62**: 138–45. https://doi.org/10.1016/j.ejca.2016.03.082
14. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; **50**: 122S–150S. https://doi.org/10.2967/jnumed.108.057307
15. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae
16. Burgart LJ, Chopp WV, Jain D. Protocol for the Examination of Specimens From Patients With Carcinoma of the Esophagus. Available from: 2021.https://documents.cap.org/protocols/Esophagus_4.2.0.0.REL_CAPCP.pdf
17. Wu AJ, Bosch WR, Chang DT, Hong TS, Jabbour SK, Kleinberg LR, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. *Int J Radiat Oncol Biol Phys* 2015; **92**: 911–20. https://doi.org/10.1016/j.ijrobp.2015.03.030
18. Lynch R, Pitson G, Ball D, Claude L, Sarrut D. Computed tomographic atlas for the new international lymph node map for lung cancer: a radiation oncologist perspective. *Pract Radiat Oncol* 2013; **3**: 54–66. https://doi.org/10.1016/j.prro.2012.01.007
19. Cleves M, Gould W, Gould WW, et al. An introduction to survival analysis using Stata. 2nd ed. College Station: Stata press 2008.
20. Tamhane AR, Westfall AO, Burkholder GA, et al. Prevalence odds ratio versus prevalence ratio: choice comes with consequences: prevalence odds ratio versus prevalence ratio. *Stat Med* 2016; **35**: 5730–35. https://doi.org/10.1002/sim.7059
21. Hardin JW. The sandwich estimate of variance. In: Fomby TB, Hill RC, eds. Maximum Likelihood Estimation of Misspecified Models: Twenty Years Later. Bingley: Emerald Group Publishing Limited 2003. 45–73. https://doi.org/10.1016/S0731-9053(03)17003-X
22. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007; **4**(10): e297. https://doi.org/10.1371/journal.pmed.0040297
23. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med* 2021; **384**: 1191–1203. https://doi.org/10.1056/NEJMoa2032125
24. Mayanagi S, Irino T, Kawakubo H, Kitagawa Y. Neoadjuvant treatment strategy for locally advanced thoracic esophageal cancer. *Ann Gastroenterol Surg* 2019; **3**: 269–75. https://doi.org/10.1002/ags3.12243
25. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335**: 462–67. https://doi.org/10.1056/NEJM199608153350702
26. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19**: 305–13. https://doi.org/10.1200/JCO.2001.19.2.305
27. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; **337**: 161–67. https://doi.org/10.1056/NEJM199707173370304
28. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; **6**: 659–68. https://doi.org/10.1016/S1470-2045(05)70288-6
29. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; **26**: 1086–92. https://doi.org/10.1200/JCO.2007.12.9593
30. Mariette C, Dahan L, Mornex F, Maillard E, Thomas P-A, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. *J Clin Oncol* 2014; **32**: 2416–22. https://doi.org/10.1200/JCO.2013.53.6532
31. Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen A-B, Friesland S, et al. A randomized clinical trial of neoadjuvant chemotherapy versus

neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016; **27**: 660–67. https://doi.org/10.1093/annonc/mdw010

32. Kato K, Ito Y, Daiko H, Ozawa S, Ogata T, Hara H, et al. A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 next study. *JCO* 2022; **40**: 238. https://doi.org/10.1200/JCO.2022.40.4_suppl.238
33. Han D, Li B, Zhao Q, Sun H, Dong J, Hao S, et al. The key clinical questions of neoadjuvant chemoradiotherapy for resectable esophageal cancer-A review. *Front Oncol* 2022; **12**: 890688. https://doi.org/10.3389/fonc.2022.890688
34. Gyawali B, Bouche G, Crisp N, André N. Challenges and opportunities for cancer clinical trials in low- and middle-income countries. *Nat Cancer* 2020; **1**: 142–45. https://doi.org/10.1038/s43018-020-0030-x
35. Kamarajah SK, Marson EJ, Zhou D, Wyn-Griffiths F, Lin A, Evans RPT, et al. Meta-Analysis of prognostic factors of overall survival in patients undergoing oesophagectomy for oesophageal cancer. *Dis Esophagus* 2020; **33**(11): doaa038. https://doi.org/10.1093/dote/doaa038
36. Miyata H, Tanaka K, Makino T, Yamasaki M, Miyazaki Y, Takahashi T, et al. The impact of pathological tumor regression and nodal status on survival and systemic disease in patients undergoing neoadjuvant chemotherapy for esophageal squamous cell carcinoma. *Ann Surg Oncol* 2018; **25**: 2409–17. https://doi.org/10.1245/s10434-018-6507-5
37. Koen Talsma A, Shapiro J, Looman CWN, van Hagen P, Steyerberg EW, van der Gaast A, et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy. *Annals of Surgery* 2014; **260**: 786–93. https://doi.org/10.1097/SLA.0000000000000965
38. Luchini C, Wood LD, Cheng L, Nottegar A, Stubbs B, Solmi M, et al. Extranodal extension of lymph node metastasis is a marker of poor prognosis in oesophageal cancer: a systematic review with meta-analysis. *J Clin Pathol* 2016; **69**: 956–61. https://doi.org/10.1136/jclinpath-2016-203830
39. Chen D, Mao Y, Zheng Y, Wen J, Song P, Xue Y, et al. Extracapsular lymph node involvement is a robust survival predictor in esophageal cancer patients: a pooled analysis. *Eur J Surg Oncol* 2021; **47**: 1875–82. https://doi.org/10.1016/j.ejso.2021.03.247
40. Luchini C, Veronese N. Extranodal extension of nodal metastasis is the main prognostic moderator in squamous cell carcinoma of the esophagus after neoadjuvant chemoradiotherapy. *J Thorac Dis* 2017; **9**: 3609–12. https://doi.org/10.21037/jtd.2017.09.36
41. Burt BM, Groth SS, Sada YH, Farjah F, Cornwell L, Sugarbaker DJ, et al. Utility of adjuvant chemotherapy after neoadjuvant chemoradiation and esophagectomy for esophageal cancer. *Ann Surg* 2017; **266**: 297–304. https://doi.org/10.1097/SLA.0000000000001954
42. Schurink B, Seesing MFJ, Goense L, Mook S, Brosens LAA, Mohammad NH, et al. YpT0N+ status in oesophageal cancer patients: location of residual metastatic lymph nodes with regard to the neoadjuvant radiation field. *Eur J Surg Oncol* 2019; **45**: 454–59. https://doi.org/10.1016/j.ejso.2018.11.011
43. Hagens ERC, Künzli HT, van Rijswijk A-S, Meijer SL, Mijnals RCD, Weusten BLAM, et al. Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: a prospective study. *Surg Endosc* 2020; **34**: 4347–57. https://doi.org/10.1007/s00464-019-07205-y
44. Hamai Y, Emi M, Ibuki Y, Kurokawa T, Yoshikawa T, Ohsawa M, et al. Distribution of lymph node metastasis in esophageal squamous cell carcinoma after trimodal therapy. *Ann Surg Oncol* 2021; **28**: 1798–1807. https://doi.org/10.1245/s10434-020-09106-0
45. Ajani JA, Correa AM, Hofstetter WL, Rice DC, Blum MA, Suzuki A, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol* 2012; **23**: 2638–42. https://doi.org/10.1093/annonc/mds210
46. Toxopeus ELA, Nieboer D, Shapiro J, Biermann K, van der Gaast A, van Rij CM, et al. Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer. *Radiother Oncol* 2015; **115**: 392–98. https://doi.org/10.1016/j.radonc.2015.04.028
47. Blum Murphy M, Xiao L, Patel VR, Maru DM, Correa AM, G Amlashi F, et al. Pathological complete response in patients with esophageal cancer after the trimodality approach: the association with baseline variables and survival-the University of Texas MD Anderson cancer center experience. *Cancer* 2017; **123**: 4106–13. https://doi.org/10.1002/cncr.30953