Pathological response to neoadjuvant chemoradiotherapy for oesophageal squamous cell carcinoma: multicentre East Asian and Dutch database comparison

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Introduction

More than 60 per cent of patients with oesophageal cancer worldwide live in East Asia, and the predominant histological type is squamous cell carcinoma. In several Asian countries, neoadjuvant chemoradiotherapy (nCRT) followed by surgery is a standard of care for locally advanced squamous cell carcinoma (OSCC). Historically, cisplatin/fluorouracil-based nCRT regimens have been used, but since the Dutch CROSS trial showed that 49 per cent of patients with OSCC have a pCR in the resection specimen, some Asian centres have adopted this carboplatin/paclitaxel-based regimen.

Although observational studies in the Netherlands and the USA investigating the outcome of the CROSS regimen outside the CROSS trial have reported comparable pCR rates, studies in East Asia showed lower pCR rates of 28–33 per cent. Differences in pCR between Western and East Asian populations may be due to differences in genetic and/or ethnic backgrounds. However, indications for nCRT also differ between countries. In Asian countries, nCRT is often reserved for more advanced tumours (cT3–4a N1–3 M0), whereas in many Western countries all locally advanced resectable tumours (cT1 N1–3 M0/cT2–4a N0–3 M0) are treated with nCRT before surgery. Besides, outcomes from clinical trials are often better than those of observational studies because clinical trials are conducted under controlled circumstances and observational studies have a higher risk of bias.

A worse response to nCRT according to the CROSS regimen in East Asian patients compared with Western patients may have resulted from differences in patient characteristics, such as age, comorbidities, and smoking history. However, a comparison of the CROSS trial with observational studies in East Asia is limited by the retrospective nature of the latter studies. Therefore, this study aimed to assess whether patients with oesophageal squamous cell carcinoma (OSCC) treated with neoadjuvant chemoradiotherapy (nCRT) in East Asia had an inferior pathological response compared with patients treated in Northwest Europe.

Methods

Patients with OSCC who underwent nCRT according to the CROSS regimen (carboplatin and paclitaxel with concurrent 41.4 Gy radiotherapy) followed by oesophagectomy between June 2012 and April 2020 were identified from East Asian and Dutch databases. The primary outcome was pCR, defined as ypT0 N0. Groups were compared using propensity score matching, adjusting for sex, Charlson Co-morbidity Index score, tumour location, cT and cN categories, interval between nCRT and surgery, and number of resected lymph nodes.

Results

Of 725 patients identified, 133 remained in each group after matching. A pCR was achieved in 37 patients (27.8 per cent) in the Asian database and 58 (43.6 per cent) in the Dutch database (P = 0.010). The rate of ypT1–4 was higher in Asian than Dutch data (66.2 and 49.6 per cent; P = 0.004). The ypT1–3 rate was 44.4 per cent in the Asian and 33.1 per cent in the Dutch data set. Clear margins were achieved in 92.5 per cent of Asian and 95.5 per cent of Dutch patients.

Conclusion

Regional differences in responses to CROSS nCRT for oesophageal cancer were apparent, the origin of which will need evaluation.
implications for future research into chemoradiation sensitivity and treatment of oesophageal cancer. Therefore, the present study aimed to compare the pathological outcomes of patients with OSCC who had been treated in East Asia with those who received treatment in Northwest Europe (outside the CROSS trial), while taking into account differences in patient, tumour, and treatment characteristics.

**Methods**

**Study design and patient selection**

This was a multicentre retrospective study. All patients with histologically proven locally advanced resectable OSCC treated with nCRT according to the CROSS regimen followed by oesophagectomy were eligible. For the East Asian data, all patients who underwent treatment at the Queen Mary Hospital (Hong Kong SAR, China), Chang Gung Memorial Hospital-Linkou (Taoyuan, Taiwan), or Shanghai Chest Hospital (Shanghai, China) were identified from local hospital databases. The Taiwan Cancer Registry was also used to identify eligible patients. Asian patients were treated between June 2012 (after the first publication of the CROSS trial) and April 2020 (start of this study).

For the Northwest European group, patients were identified from the Dutch Upper Gastrointestinal Cancer Audit (DUCA) database. This annually updated surgical registry includes all patients for whom potentially curative upper gastrointestinal surgery is planned in the Netherlands. The database registers which neoadjuvant scheme is given (CROSS), but not the exact chemotherapeutic agents. To ensure that all patients included in the present study underwent nCRT according to CROSS, only patients who started nCRT after CROSS had been adopted as the sole standard of care for nCRT in the Netherlands were included. Thus, Dutch patients treated from January 2014 (update of Dutch national guidelines) to December 2019 (final date in the 2020 DUCA database) were included in this study.

Excluded were patients who completed less than 80 per cent of an nCRT regimen, those who had no pathological staging data available, and patients with an interval between nCRT and surgery of less than 6 months, or for whom the interval was unknown. Chemotherapy dose reduction was not considered to represent failure to complete the cycle. Patients with fewer than 15 resected lymph nodes were also excluded to reduce the risk of inaccurate pathological nodal staging.

At Shanghai Chest hospital, all patients provided written informed consent for prospective data collection. At Queen Mary Hospital and Chang Gung Memorial Hospital, the local medical ethics committees approved retrospective data collection. Dutch data were registered anonymously, so informed consent and ethical review were not required under Dutch law. The study protocol was approved by the DUCA Scientific Committee.

**Neoadjuvant treatment**

The CROSS nCRT regimen consisted of five weekly cycles of intravenous carboplatin (area under the curve 2 mg per ml per min) and paclitaxel (50 mg per m² body surface area) administered on the first day of each week. Concurrently, 23 daily fractions of 1.8 Gy external-beam photon radiation was administered for 5 days per week, starting on the first day of each cycle, up to a total dose of 41.4 Gy. The primary tumour and all enlarged regional lymph nodes were delineated as gross tumour volumes (GTVs). Variation may exist among protocols of different participating centres; however, in general, GTV to planning target volume margins of 1.5 cm radially and 4 cm longitudinally are adopted. If the tumour extends into the stomach, a distal margin of 3 cm instead of 4 cm is used. In the Asian and Dutch centres, a three-dimensional conformal, intensity-modulated radiation technique or volumetrically modulated arc therapy was used during the inclusion period for this study. Some patients treated at Chang Gung Memorial Hospital received one extra cycle of carboplatin (area under the curve 2 mg per ml per min) and paclitaxel (50 mg per m² body surface area) 1 week before the start of nCRT.

**Surgery**

Surgical resection was preferably performed within 12 weeks of the completion of chemoradiotherapy. All centres, transthoracic oesophagectomy with two-field lymphadenectomy was the preferred procedure. Three-field lymphadenectomy was undertaken in patients with suspected cervical lymph nodes. For patients with a junctional tumour or in poor preoperative condition, transhiatal oesophagectomy could be performed to limit surgical trauma. A gastric tube was preferred for reconstruction of the gastrointestinal tract. Surgery was carried out using a minimally invasive, hybrid minimally invasive, or open surgical technique.

**Histopathological analysis**

Histopathological analysis of the resection specimens was done according to local protocols. In all centres, resection specimens were assessed macroscopically for residual tumour. Suspicous areas and their surroundings were embedded in paraffin. Sections of 3.5–5 μm were stained with haematoxylin and eosin, and the presence of residual vital tumour cells was assessed microscopically. Immunohistochemistry was used only if there was uncertainty regarding atypical cells or undetected isolated tumour cells. If there was residual tumour, the differentiation grade and distance to the proximal, distal, and circumferential resection margins were described. In addition, the number of resected lymph nodes and number of lymph nodes containing malignant cells, histological regression (signs of regression and/or presence of vital tumour cells), and pathological TNM stage after nCRT (ypTNM) according to the seventh edition of the UICC Cancer Staging Manual were recorded.

**Outcomes**

The primary outcome was pCR, as it is a direct marker of the response to nCRT and is not affected by other adjuvant therapies; pCR was defined as pathological stage ypT0 N0.

Secondary outcomes were pathological T and N categories, number of positive lymph nodes, histological regression, and microscopic radicality of the resection. Histological tumour regression was categorized as no response (no signs of regression), partial response (signs of regression, but vital tumour cells present in the primary tumour and/or lymph nodes), or complete response (no vital tumour cells at the site of the primary tumour and in lymph nodes). A microscopically radical (R0) resection was defined as a resection with tumour-free (more than 0 mm) proximal, distal, and circumferential resection margins.

**Statistical analysis**

Continuous variables are presented as mean(s.d.), or median (i.q.r.) for non-normally distributed values (assessed by visual inspection of histograms and Shapiro–Wilk test if unclear). Student’s t test was used to compare normally distributed values and the Kruskal–Wallis test for those with a non-normal
distribution. Categorical variables are presented as numbers with percentages and were compared using the χ² test. Fisher’s exact test was used when the expected cell counts were below five or when two categorical variables were compared.

Propensity score matching using the nearest-neighbour method without replacement, with a 1:1 ratio and a caliper of 0.20, was employed to reduce the impact of potentially confounding factors. Propensity scores were based on the following potentially confounding factors: sex, Charlson Co-morbidity Index (CCI) score, tumour location, clinical T category and clinical N category according to the seventh edition of the UICC Cancer Staging Manual, interval between start of nCRT and surgery, and number of resected lymph nodes. These confounding factors were selected through consensus discussions between expert upper gastrointestinal surgeons. As all matching variables had less than 5 per cent missing data, a complete-case analysis was undertaken to handle missing data in the matching variables.

Statistical significance was defined as P<0.050 (2-sided). All analyses were performed using the tableone, Matchit, and stats packages in R version 3.6.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 189 eligible patients were identified from the East Asian databases and 725 from the Dutch database. Of the Asian patients, 14 (7.4 per cent) completed less than 80 per cent of nCRT, 2 (1.1 per cent) had an unreliable interval from nCRT to surgery, and 21 (11.1 per cent) had fewer than 15 lymph nodes removed. Of the 725 Dutch patients, 24 (3.3 per cent) completed less than 80 per cent of nCRT, 15 (2.1 per cent) had an unreliable interval from nCRT to surgery, 111 (15.3 per cent) had fewer than 15 lymph nodes removed, and 2 (0.3 per cent) had no available pathological data. Eventually, 152 and 573 patients were included in the Asian and Dutch data sets respectively (Fig. 1).

Before matching, East Asian patients were more likely to be men, have a lower CCI, have tumours in the proximal or middle oesophagus, and have a higher clinical T and N categories. In addition, the interval between the start of nCRT and surgery was shorter and more lymph nodes were resected during surgery in Asian patients. After matching, 133 patients remained in each cohort (266 patients in total), and no statistically significant differences were observed in the matched variables between groups. In the Asian cohort, 21 of 133 patients (15.8 per cent) received six cycles had a pCR compared with 58 of 133 (43.6 per cent) in the Dutch cohort (P=0.010). Eight of 21 Asian patients (38.1 per cent) who received six cycles had a pCR compared with 29 of 112...

Fig. 1 Flow chart showing patients who underwent neoadjuvant chemoradiotherapy followed by oesophagectomy in the Asian and Dutch cohorts. Patients with data missing for at least one matching variable. nCRT, neoadjuvant chemoradiotherapy.
The pathological T category was higher in the Asians than in the Dutch. (Table 3). Forty-five of 133 Asian patients (33.8 per cent) had ypT0 disease compared with 67 of 133 Dutch patients (50.4 per cent). The pathological N status was poorer in Asia compared with the Netherlands. The overall pCR rate in the Asian cohort was 35.7 per cent, with 27.8 per cent in the matched cohort, compared with 37 per cent in the Dutch cohort and 43.6 per cent in the Dutch matched cohort (P = 0.010). The overall ypT0 rate in the Asian cohort was 11.7 per cent, compared with 21.5 per cent in the matched cohort, 10.7 per cent in the Dutch cohort, and 14 per cent in the Dutch matched cohort (P = 0.004). The overall ypN0 rate in the Asian cohort was 61.3 per cent, compared with 75.5 per cent in the matched cohort, 69.9 per cent in the Dutch cohort, and 86.9 per cent in the Dutch matched cohort (P = 0.239).

Values are n (%) unless otherwise indicated. *χ2 or Fisher’s exact test, except †Kruskal–Wallis test.

Values are n (%) unless otherwise indicated. †According to the seventh edition of the UICC Cancer Staging Manual [13]. §Microscopically radical. *χ2 or Fisher’s exact test, except †Kruskal–Wallis test.
comparable in the two cohorts \( (P = 0.239) \) (Table 3). In the Asian group, 74 of 133 patients \( (55.6 \text{ per cent}) \) had ypNO disease, compared with 89 of 133 \( (66.9 \text{ per cent}) \) in the Dutch cohort. R0 resection rates were similar in the Asian and Dutch patients \( (92.5 \text{ versus } 95.5 \text{ per cent}; \ P = 0.440) \). There was also no significant difference in histological grade between the two cohorts \( (P = 0.103) \). Of the Asian group, 53 patients \( (39.8 \text{ per cent}) \) had well or moderately differentiated tumours, and 20 \( (15.0 \text{ per cent}) \) had poorly differentiated or undifferentiated tumours. In the Dutch group, 41 patients \( (30.8 \text{ per cent}) \) had well or moderately differentiated tumours, and 19 \( (14.3 \text{ per cent}) \) had poorly differentiated or undifferentiated tumours. Pathological characteristics of the unmatched groups are shown in Tables S1 and S2.

**Discussion**

The present study showed that patients with OSCC treated in East Asia had less of a response to nCRT using the CROSS regimen than those treated in the Netherlands, regardless of differences in patient, tumour, and treatment characteristics. This suggests that other factors also have an effect on treatment response. The response to nCRT in the primary tumour was significantly worse in the Asian group, whereas the response in regional lymph nodes was not significantly different. The inferior response in the Asian cohort did not affect the R0 resection rate, which was comparable between the Asian and Dutch cohorts.

Differences in response to anticancer therapy between Asian and Western patients have been related to varying frequencies of genetic polymorphisms that affect drug metabolism and DNA repair. A difference in response to carboplatin and paclitaxel among Asian patients compared with Western patients with lung cancer has been linked to variants of the cytochrome enzyme CYP3A4 and nucleotide excision repair enzyme ERCC2. In contrast to the present findings, however, Asian patients in these studies seemed to respond better, which may indicate that other factors also affected the response. In Western patients with oesophageal cancer, a better response to chemoradiotherapy has been linked to variants of the nucleotide excision repair enzyme ERCC1. These variants may either decrease resistance to radiotherapy or increase sensitivity to platinum-based chemotherapy. Varying toxicity between East Asian and Western patients has also been linked to ethnic differences in genotype. In the present study, 7.4 per cent of Asian patients could not complete at least 80 per cent of nCRT, compared with 3.3 per cent of Dutch patients. This could also be explained by differences in toxic side-effects. However, the exact effects of genetic differences on response to anticancer therapies between patients of different ethnic backgrounds have not yet been elucidated. The recent NCCRT100 randomized trial investigated neoadjuvant vinorelbine and cisplatin with concurrent 40 Gy radiotherapy in Asian patients with OSCC, which yielded a pCR rate of 43 per cent. Yet, grade 3–4 haematological toxicity was relatively common \( (54 \text{ per cent}) \), and overall compliance with the total chemotherapy dose was 57 per cent at most \( (\text{versus } 8 \text{ and } 91 \text{ per cent} \ \text{respectively in the CROSS trial}) \). Further research into genetic differences between large ethnic groups (such as Asian and Caucasian populations) may lead to better personalized treatments and improved outcomes for patients with oesophageal cancer around the world.

Non-genetic ethnic differences have also been related to the effectiveness of chemo(radio)therapy. The composition of the gut microbiome has been associated with response to anticancer therapy for different types of cancer, including gastrointestinal cancers. The gut microbiome is influenced by environmental factors such as diet, smoking, and alcohol consumption. Even in ethnic groups that share the same geographical location, compositions of the gut microbiome vary. In addition, environmental factors such as smoking may have a direct effect on cellular resistance to specific chemotherapeutic agents.

To the best of the authors’ knowledge, this is the first study to directly compare the effectiveness of a specific neoadjuvant regimen in different ethnic groups with oesophageal cancer. The large group of Dutch patients allowed a good matching balance and adjustment for well known confounding factors. However, several limitations should be mentioned. The retrospective nature of this study introduced risks of bias such as varying pretreatment staging protocols. Other factors may have also affected the pCR rates reported in this study. Tumour length, lymph node stations in which positive nodes were identified before treatment, and stations that were surgically dissected were not registered. In addition, differences in pathological assessment (such as in the number of sections or additional immunohistochemistry) may have had an effect on the detection of residual tumour cells. Although uniform treatment protocols were used, slight differences in treatment may also have contributed to different responses to nCRT. Patients with suspected lymph nodes far from the primary tumour and outside the maximum tolerated radiation field are considered ineligible for nCRT and are treated with induction or palliative chemotherapy in most Dutch centres. In some Asian centres, these lymph nodes may have been irradiated using skipped field irradiation (using 2 or more smaller radiation fields). The effect of this difference in treatment may be observed in the present study, as no significant difference in response was observed in the regional lymph nodes, whereas the response of the primary tumour was significantly worse in the Asian cohort. Furthermore, 15.8 per cent of the patients in the Asian cohort had six instead of five chemotherapy cycles. The effect of this extra cycle on pCR was limited and in favour of the Asian cohort. Most of the factors that could have had an effect on pCR, but for which adjustment was not made, are associated with response (assessment) in the lymph nodes. The substantial difference in ypT category indicates that the response to nCRT according to the CROSS regimen may be worse in East Asian patients.

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**Disclosure**

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Supplementary material

Supplementary material is available at BJS online.

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Monday, 28 November 2022

09.50 Opening and welcome
Jochen Lange, St.Gallen, CH

10.00 It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30 Predictive and diagnostic markers of anastomotic leak
Andre D’Hoore, Leuven, BE

11.00 SATELLITE SYMPOSIUM
ETHICON

11.45 Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15 LUNCH

13.45 Operative techniques to reduce anastomotic recurrence in Crohn’s disease
Laura Hancock, Manchester, UK

14.15 Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christian Buskens, Amsterdam, NL

14.45 To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15 COFFEE BREAK

15.45 Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15 SATELLITE SYMPOSIUM
Medtronic

17.00 Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30 EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00 Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00 CONSULTANT’S CORNER
Michel Adamina, Winterthur, CH

10.30 COFFEE BREAK

11.00 SATELLITE SYMPOSIUM
INTUITIVE

11.45 Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15 LUNCH

13.45 VIDEO SESSION

14.15 SATELLITE SYMPOSIUM

15.00 COFFEE BREAK

15.30 The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30 SATELLITE SYMPOSIUM

17.15 Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Wednesday, 30 November 2022

9.00 Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30 Predictors for Postoperative Complications and Mortality
Ronan O’Connell, Dublin, IE

10.00 Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30 COFFEE BREAK

11.00 Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

12.00 Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30 LUNCH

14.00 Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30 Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00 SATELLITE SYMPOSIUM

15.45 COFFEE BREAK

16.15 Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45 Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15 Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30 FESTIVE EVENING

Thursday, 1 December 2022

Masterclass in Colorectal Surgery
Proctology Day

Information & Registration www.colorectalsurgery.eu