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Original Article

Detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal squamous cell carcinoma: prospective multicentre preSINO trial

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Abstract

Background: Neoadjuvant chemoradiotherapy (nCRT) in patients with oesophageal squamous cell carcinoma (OSCC) may lead to clinical complete response (cCR). It is important to know the accuracy of clinical response evaluations (CREs) before advocating active surveillance instead of oesophagectomy.

Methods: This was a prospective, multicentre study of patients with locally advanced OSCC. They received the first CRE (bite-on-bite biopsies) 4–6 weeks after nCRT. Patients with residual tumour underwent surgery. Patients with a cCR at CRE-1 underwent a second CRE 10–12 weeks after nCRT using PET-CT, bite-on-bite biopsies and endoscopic ultrasound fine-needle aspiration (EUS-FNA). All patients without distant metastases underwent surgery. Primary endpoint was the accuracy of CREs for detecting Tumour Regression Grade (TRG)3–4 or TRG1–2 with ypN+ residual tumour with a prespecified false-negative rate (FNR) of 19.5%. Circulating-tumour DNA (ctDNA) at CREs was performed for exploratory analysis.

Results: In total 309 patients were included. Eighteen of 133 patients with TRG3–4 or TRG1–2 with ypN+ residual tumours were not detected by bite-on-bite biopsies and EUS-FNA (FNR: 13.5%). Sensitivity, specificity, negative predictive value and positive predictive value of detecting any residual tumour were 81.7%, 93.2%, 68.7% and 96.5% respectively. PET-CT detected interval distant metastases in 13 (4.9%) of 268 patients presurgically. After a minimum 12-month follow-up, systemic recurrence rates were 28.0% in patients with positive ctDNA at CREs and 5.3% in those with negative ctDNA.

Conclusions: Bite-on-bite biopsies and EUS-FNA were accurate in detecting residual disease after nCRT in OSCC. Positive ctDNA at CREs may indicate an increased risk of systemic metastases.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by oesophagectomy is standard treatment for locally advanced oesophageal squamous cell carcinoma (OSCC)[1,2]. More than 40% of patients with OSCC treated with nCRT have a pathological complete response (pCR). The benefit of surgery in these patients can be questioned. Oesophagectomy is associated with substantial rates of morbidity or mortality[3,4]. Hence, active surveillance for patients with a clinically complete response (cCR) after nCRT may be a valid alternative strategy[5].

Active surveillance means that surgery is performed only when a locoregional tumour is detected after nCRT[6]. The preSANO trial[7] showed that the combination of endoscopy with bite-on-bite biopsies, endoscopic ultrasound fine-needle aspiration (EUS-FNA) of suspicious lymph nodes and PET-CT was sufficiently accurate in detecting residual locoregional tumour and distant metastases after nCRT. Based on these results, active surveillance has been investigated in the randomized SANO trial[5,8]. This study mainly included patients with adenocarcinoma and demonstrated non-inferior survival for patients who underwent active surveillance compared to standard surgery.

Approximately 80% of patients with oesophageal cancer in the world have OSCC and are diagnosed in East Asia. OSCC has different genetic alterations and as such the biological behaviour differs from adenocarcinoma[9]. Whether findings of the preSANO and SANO trials are also valid for patients with OSCC remains to be determined. In addition, the advent of liquid biopsy of circulating-tumour DNA (ctDNA) shows promise in reflecting molecular residual disease (MRD) and disease surveillance in

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non-metastatic cancers[10,11]. There is a potential role for using ctDNA to detect systemic disease and integrate into an organ-preserving strategy for oesophageal cancer[12,13].

This preSINO trial[14] (pre-Surgery If Needed for Oesophageal cancer) aimed to assess the accuracy of clinical response evaluations (CREs) with bite-on-bite biopsies, EUS-FNA and PET-CT after nCRT in patients with OSCC. Additionally, this trial included ctDNA MRD detection as an exploratory study to evaluate the clinical validity of ctDNA testing during CREs for recurrence prediction.

Methods

Patients

This prospective, multicentre, diagnostic cohort study was conducted at three high-volume Asian centres including Shanghai Chest Hospital (Shanghai, China), Queen Mary Hospital (Hong Kong, China), and Chang Gung Memorial Hospital-Linkou (Taiwan, China). This study was registered at ClinicalTrials.gov (NCT03937362). The study protocol has been published previously[14]. Patients with locally advanced OSCC who were assigned to undergo nCRT according to the CROSS regimen and surgical resection were considered eligible for the study. The study protocol was approved by the medical ethics committee of the Shanghai Chest Hospital (KS1913, 26 February 2019). All patients provided written informed consent.

Study procedures

The study profile is shown in *Fig. 1*. All patients underwent clinical staging at baseline, including endoscopy with biopsy, CT scan and PET-CT. Neoadjuvant therapy consisted of five weekly cycles of carboplatin at an area under the curve (AUC) of 2 mg/ml/min and paclitaxel at a dose of 50 mg/m^2 on days 1, 8, 15, 22 and 29 with concurrent 41.4 Gy radiotherapy given in 23 fractions of 1.8 Gy, five fractions per week, starting at the day of the first cycle of chemotherapy. Patients underwent a first clinical response evaluation (CRE-1) 4–6 weeks after completion of nCRT, which included endoscopy with at least four bite-on-bite biopsies. In case of residual locoregional disease, CRE-1 was considered positive and patients were planned for immediate oesophagectomy if no distant metastases were present on PET-CT. If no residual tumour was detected, surgery was postponed for another 6 weeks until the second clinical response evaluation (CRE-2). CRE-2 consisted of PET-CT scan, followed by bite-on-bite biopsies and EUS-FNA for suspected lymph nodes. All patients without distant metastases underwent surgery after CRE-2.

Pathology assessment

The resected specimens were reviewed by an experienced pathologist in each centre according to standard protocol. Tumour cells were considered vital if their cytomorphological integrity was intact. The Chirieac tumour regression grade (TRG) system[15] was used to classify pathological response into four grades including no residual tumour cells (TRG1), 1–10% residual tumour cells (TRG2), 11–50% residual tumour cells (TRG3), and more than 50% residual tumour cells (TRG4). All negative preoperative biopsies in patients with TRG3-4 or TRG1-2 with ypN + residual tumours were reviewed.

Study endpoints

It was hypothesized that for an organ-preserving strategy in a future prospective trial, TRG2 residual disease could be safely missed because the tumour would likely be detected at a resectable stage during subsequent active surveillance based on the preSANO trial[7]. However, ypT0N+ disease after nCRT tends to occur more frequently in patients with OSCC than in patients with adenocarcinoma[16]. Delayed detection or progression of higher-risk residual disease (TRG3-4 or TRG1-2 with ypN+) could render surgery unfeasible and increase risk of distant dissemination. Therefore, the primary endpoint was the diagnostic accuracy for detecting TRG3–4 or TRG1–2 with ypN+ residual disease in order to prevent short-term loss of resectability and minimize the risk of long-term distant dissemination. Numbers of true-positives, false-positives, true-negatives and false-negatives were calculated. Secondary endpoints were sensitivity, specificity, negative predictive value and positive predictive value for predicting any residual disease.

Sample size

Sample size calculation was described in the protocol[14]. In the preSANO trial[7], a 10% false-negative rate (FNR) for detecting TRG3–4 residual disease (regardless of lymph node status) was assessed. The acceptable FNR was increased from 10% to 12% due to the additional assessment of TRG1–2/ypN+ residual disease. In a large Dutch cohort of patients who received nCRT following the CROSS regimen (not published data), 294 of 616 patients had TRG3–4 residual disease. If a 12% missing rate was allowed for detecting TRG3–4 or TRG1–2/ypN+ residual disease, 35 patients could be missed. Accordingly, CREs of 5.7% (35 of 616 patients) would be allowed to be false-negative. In this cohort, 138 of 616 patients had OSCC, and 40 of these 138 patients had TRG3–4 residual disease. Applying the same FNR of 5.7% to this subgroup, it would be allowed to miss 7.8 of these 138 patients. Hence, the FNR of 19.5% (7.8 of 40 patients) for detecting TRG3–4 or TRG1–2 with ypN+ residual disease would be acceptable. To determine a sensitivity of 80.5% for the CREs with a power of 80% and a significance level of 5%, a sample size of 133 patients with TRG3–4 or TRG1–2 with ypN+ residual disease was required. As 34% of OSCC patients showed TRG3–4 or TRG1–2 with ypN+ residual disease after nCRT[1], assuming a 15% drop-out rate, 460 patients had to be enrolled in the study. During a predefined interim analysis after 200 patients, 59% of patients had TRG3–4 and TRG1–2 with ypN+ residual disease. The sample size was amended to 290 patients.

Exploratory analysis

It was hypothesized that local assessment methods (bite-on-bite biopsies and EUS-FNA) may not adequately reflect systemic residual disease. Analyses of ctDNA were performed in patients with available blood samples. ctDNA was quantified using a tumour-informed assay using the Patient-specific Prognostic and Potential Therapeutic Marker Tracking (brPROPHET®, Burning Rock Biotech, Guangzhou, China) approach to assess residual disease after nCRT. At baseline, tumour tissue from formalin-fixed paraffin-embedded (FFPE) samples and matched white blood cells before nCRT were whole-exome sequenced (WES) for patient-specific somatic variants. A personalized panel for ctDNA was designed. Serial peripheral blood samples (20 ml) were analysed at three time points (baseline, CRE-1, and CRE-2) for ctDNA detection.

The ctDNA tests were conducted in a single centre (Burning Rock Biotech, Guangzhou, China). Briefly, patient-specific somatic variants were identified by WES analysis of the baseline tumour and paired white blood cells. For a given set of variants, up to 50 highly ranked variants with a variant allele frequency ≥ 3.0% were selected for panel design. The personalized capture probe based

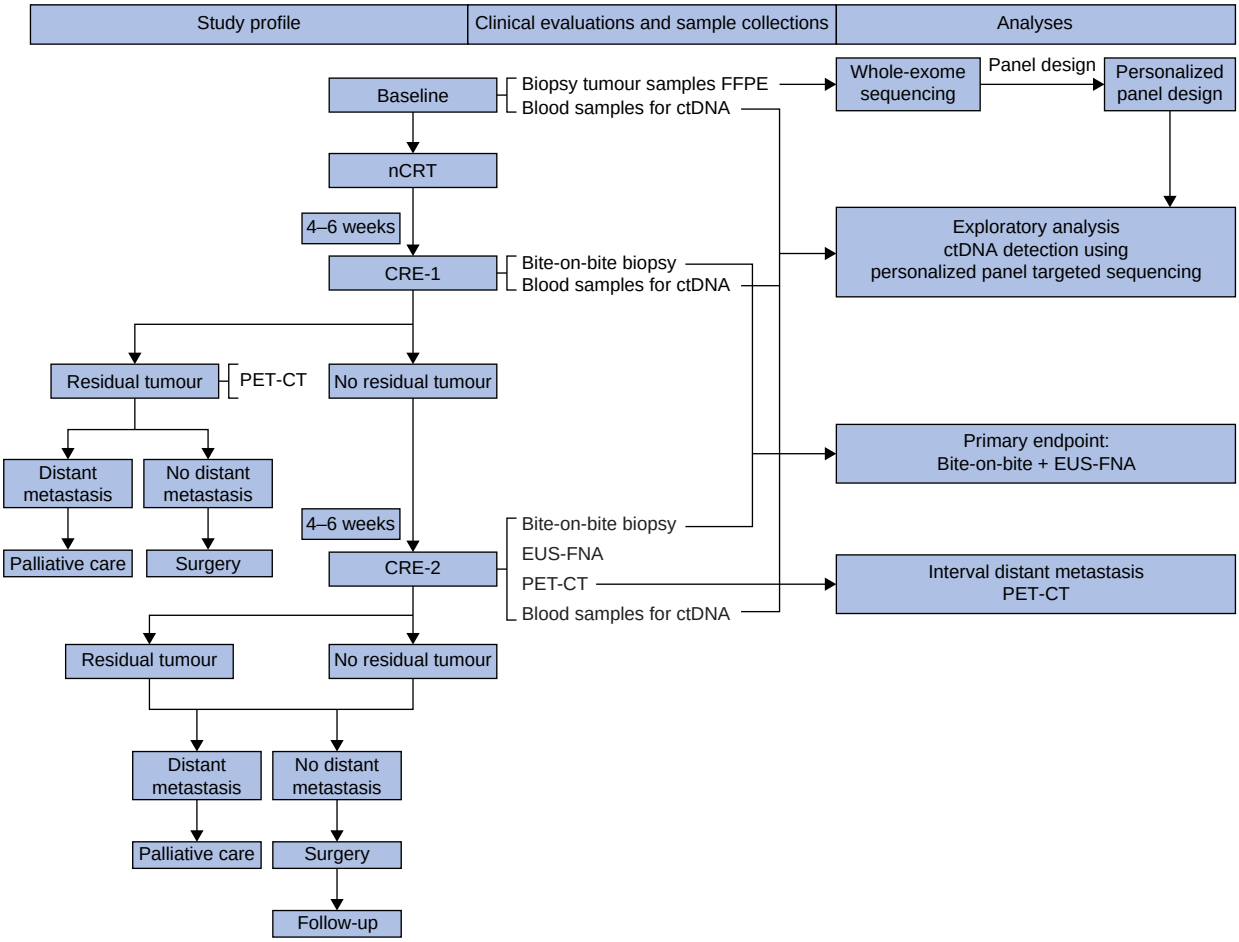

Fig. 1 Study profile

CRE-1, first clinical response evaluation, 4–6 weeks after completion of nCRT; CRE-2, second clinical response evaluation, 10–12 weeks after completion of nCRT; ctDNA, circulating tumour DNA; EUS-FNA, endoscopic ultrasound fine-needle aspiration; FFPE, from formalin-fixed paraffin-embedded; nCRT, neoadjuvant chemoradiotherapy

next-generation sequencing panel was used to track patient-specific and tumour-specific variants. Blood samples were considered ctDNA-positive if the baseline tumour personalized mutation panel could be matched with the same specific mutation in ctDNA of peripheral blood. Details of cell-free DNA extraction, library construction, panel design, next-generation sequencing and defining mutations were described previously[17].

Statistical analysis

Patients who did not complete neoadjuvant treatment or who withdrew consent and those with missing index tests because of protocol violation or death before CREs were excluded from analyses. Continuous variables are presented as median (i.q.r.) and categorical variables are presented as numbers with percentages. Kruskal–Wallis test was used for intergroup comparisons of continuous variables, whereas chi-square test or Fisher's exact test was used to compare categorical data. A Z-test was performed to assess whether the observed FNR was significantly lower than the predefined target FNR. Ninety-five percent confidence intervals were calculated according to the Wilson procedure, without a correction for continuity. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for TRG2, TRG3, TRG4 and ypN+ combined *versus* TRG1–ypN0. Patients with TRG2–ypN0 tumours were not excluded from sensitivity, specificity, negative predictive value and positive predictive value analyses because this would bias results. A significance level of 0.05 was used, based on two-sided tests. All analyses were performed in SPSS (version 26.0, IBM, Chicago, Illinois, USA) and R (version 4.3.0, R Foundation, Vienna, Austria).

Results

Patients

Between August 2019 and January 2023, 309 patients were eligible for enrolment. Nine patients were excluded (*Fig. 2*). Of 300 patients who underwent CREs, 242 had bite-on-bite biopsies and EUS-FNA followed by surgery and were included in the final analysis. Of 300 patients who underwent CREs, 268 (89.3%) were included in PET-CT analysis (*Fig. S1*) and 132 (44.0%) were included in ctDNA analysis (*Fig. S2*). Baseline characteristics of all patients are shown in *Table 1*.

Accuracy of bite-on-bite biopsies and EUS-FNA

Among the 242 patients in the final analysis, pathological responses are presented in *Table S1*. Of them, 143 (59.1%) had positive bite-on-bite biopsies or EUS-FNA, or non-traversable tumours in endoscopy at CRE-1 or CRE-2. Of the 133 patients who had TRG3–4 or TRG1–2 with ypN+ residual disease, 18 had a false negative CRE leading to a FNR of 13.5% (95% c.i.

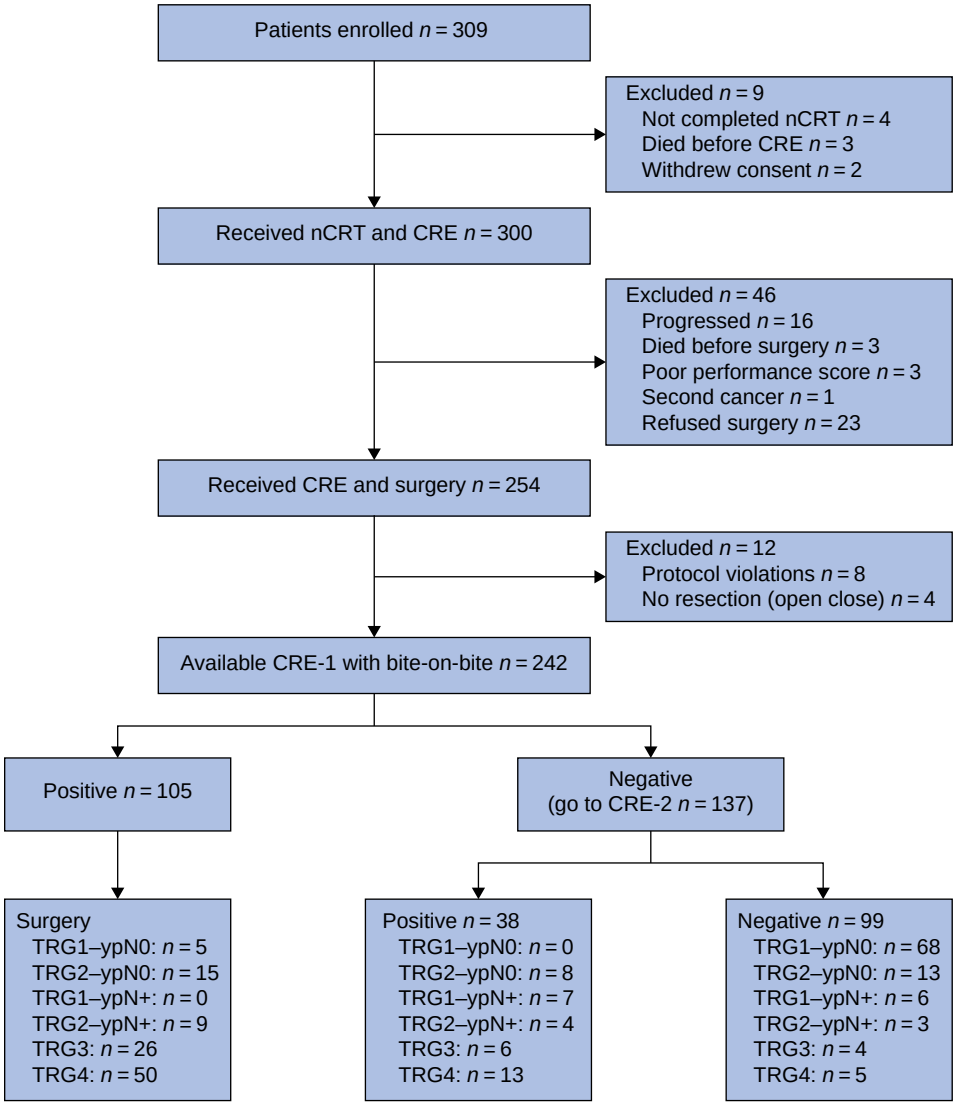

Fig. 2 Flow chart of bite-on-bite biopsy and EUS-FNA

CRE, clinical response evaluation; nCRT, neoadjuvant chemoradiotherapy

Table 1 Baseline characteristics of all enrolled patients

	(*n* = 309)
Age (years)*	65 (62–70)
Sex	
F	41
M	268
Tumour location	
Upper	33 (10.7)
Middle	160 (51.8)
Lower	116 (37.5)
Clinical T category	
cT1	1 (0.3)
cT2	26 (8.4)
cT3	252 (81.6)
cT4	30 (9.7)
Clinical N category	
cN0	62 (20.1)
cN1	173 (55.9)
cN2	71 (23.0)
cN3	3 (1.0)

Values are *n* (%) unless otherwise indicated. *Values are median (i.q.r.).

8.7 to 20.4; *Fig. 3*), which was lower than the predefined maximum FNR of 19.5% ($P = 0.041$). The sensitivity, specificity, negative predictive value and positive predictive value of TRG2–4 or ypN+ *versus* TRG1–ypN0 were 81.7% (138 of 169), 93.2% (68 of 73), 68.7% (68 of 99), and 96.5% (138 of 143) respectively (*Table 2*).

Of the five patients with TRG1 and who had false-positive results (FPR, 6.8%), four were endoscopically non-traversable due to stenosis and one had high-grade dysplasia. Eleven patients (4.5%) showed non-traversable stenosis at CRE-1, of whom four patients had pathological results of complete response (TRG1), one patient had TRG2, one patient had TRG3, and five patients had TRG4 residual disease. Nine of 104 patients had negative bite-on-bite biopsies and EUS-FNA despite having TRG3–4 residual disease (8.7%), whereas for the 29 patients who had TRG1–2 with ypN+ residual disease, nine had negative results of bite-on-bite biopsies and EUS-FNA (31.0%), and six of the 29 patients were detected by EUS-FNA although with negative bite-on-bite biopsies. Among the 53 patients who underwent EUS-FNA for suspicious lymph nodes

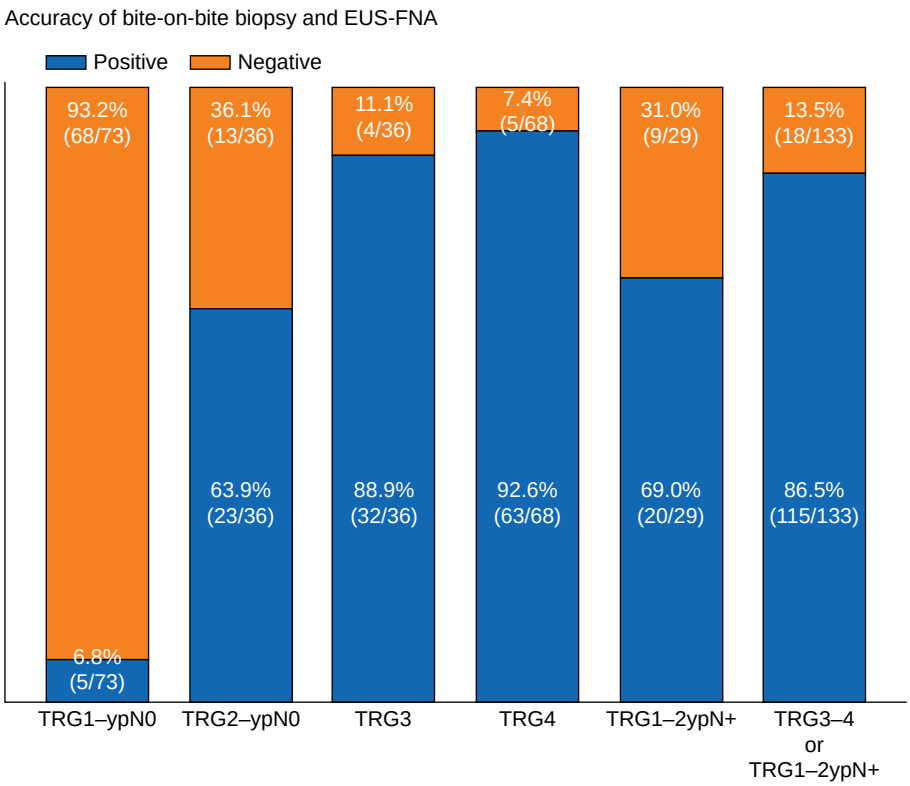

Fig. 3 Outcomes of CREs with bite-on-bite biopsy and EUS-FNA

CRE, clinical response evaluation; EUS-FNA, endoscopic ultrasound fine-needle aspiration; TRG, tumour regression grade

Table 2 Diagnostic accuracy of bite-on-bite biopsies and EUS-FNA

	Bite-on-bite + EUS-FNA
False-negative rate*	13.5 (8.7–20.4)
Sensitivity†	81.7 (75.1–86.8)
Specificity†	93.2 (84.9–97.0)
Negative predictive value†	68.7 (59.0–77.0)
Positive predictive value†	96.5 (92.1–98.5)

Values are % (95% c.i.). EUS-FNA, endoscopic ultrasound fine-needle aspiration. *Calculated as the proportion of tumour regression grade (TRG)3–4 or TRG1–2/ypN+ residual disease missed during clinical response evaluations. †Accuracy estimates were calculated for predicting TRG2–4 or ypN+ *versus* TRG1–ypN0 during clinical response evaluations.

as determined by PET-CT or EUS, nine had residual disease in lymph nodes (*Table S2*).

PET-CT analysis

Of the 309 enrolled patients, 268 (86.7%) were included in the analysis of distant metastases (41 patients without follow-up scans were excluded). PET-CT detected interval distant metastases in 4.9% (13 of 268) of patients before surgery (*Fig. S2*). In five patients, distant metastases were detected before surgery at CRE-1 and in 8 patients before surgery at CRE-2. Sites of interval distant metastases included the lung ($n = 5$), liver ($n = 3$), bone ($n = 2$), brain ($n = 1$), both liver and bone ($n = 1$), and supraclavicular lymph nodes ($n = 1$).

Exploratory analysis of ctDNA

Baseline characteristics and pathological regression grades were comparable between the ctDNA cohort consisting of 132 patients and the overall cohort (*Table S3*). ctDNA was detected in 131 of 132 pre-nCRT plasma samples (99.2%) at baseline. After nCRT, 75 patients were ctDNA-positive and 57 patients were ctDNA-negative at CRE-1 or CRE-2. Of the 74 patients who had TRG3–4 or TRG1–2 with ypN+ residual disease, 16 were ctDNA-negative leading to a FNR of 21.6% (*Table S4*). When adding ctDNA to bite-on-bite biopsies with EUS-FNA, FNR was reduced from 14.9% to 5.4%. After a minimum follow-up of 12 months, distant metastases were seen in 21 of 75 patients (28.0%) who were ctDNA-positive compared to three of 57 patients (5.3%) with negative ctDNA. Subgroup analysis showed that regardless of whether the CRE was negative or positive based on endoscopy and EUS, the rate of distant metastases in ctDNA-positive patients was higher than that in ctDNA-negative patients (19.0% *versus* 2.7% and 31.5% *versus* 10.0% respectively; *Fig. S3*).

Discussion

In patients with OSCC, the diagnostic accuracy of endoscopy with bite-on-bite biopsies and EUS-FNA of suspicious lymph nodes to detect residual disease after nCRT was acceptable, missing 13.5% of TRG3–4 or TRG1–2 with ypN+ residual locoregional disease. The prespecified primary endpoint of the study was met. PET-CT detected interval distant metastases in 4.9% of patients before planned surgery. Positive ctDNA after nCRT during CREs may indicate an increased risk of systemic recurrence, potentially serving as a diagnostic tool to identify patients who would benefit from postponement of surgery and additional systemic therapy. These results justify the initiation of a SINO trial in which overall survival of cCR patients after

nCRT undergoing active surveillance will be compared to immediate surgery.

Previous studies have tried to establish the optimal composition of diagnostic modalities to detect residual disease after neoadjuvant treatment for oesophageal cancer. However, most studies were retrospective and examined a single modality[18–20]. The preSANO trial[7] reported that 90.0% of TRG3–4 residual tumour could be accurately detected with endoscopy with bite-on-bite biopsies and EUS-FNA. Based on these results, the SANO trial[5] was initiated to compare active surveillance *versus* standard surgery in patients with a cCR after nCRT. The SANO demonstrated a non-inferior overall and disease-free survival for active surveillance compared to standard surgery. According to the SANO study, at least 35% of patients with a cCR who underwent active surveillance could be spared an oesophagectomy. These data confirmed the efficacy of CREs within a prospective study on active surveillance, providing a future direction for organ-preserving strategy in oesophageal cancer.

However, OSCC in Asia that make up more than half of the world's burden of oesophageal cancer, exhibits a different biological behaviour compared to adenocarcinoma, including extensive lymph node metastases[21,22] and a worse treatment response to nCRT[9]. Therefore, the present study focused on OSCC and patients with TRG1–2/ypN+ were included. The same diagnostic modalities used in the preSANO study had a fairly high accuracy in detecting residual tumour in patients with OSCC after nCRT. Even though the pCR rate of the overall cohort was 30%, which was significantly lower than 49% in the CROSS trial[1], the efficacy of bite-on-bite biopsies for detecting residual disease at the primary tumour site was confirmed. The FNR of bite-on-bite biopsies and EUS-FNA in detecting TRG3–4 or TRG1–2 with ypN+ residual disease was 13.5%, which was lower than the estimated maximum FNR (19.5%) to proceed with a randomized SINO trial in OSCC patients from Asia.

An organ-preserving strategy should ideally meet with the following prerequisites. It must provide effective neoadjuvant therapy for locoregional disease control. Accurate detection of systemic disease is important to avoid surgery, even when an apparent cCR is achieved for locoregional disease. Although PET-CT has value in identifying distant metastases and thereby avoiding oesophagectomy in some patients, it remains clinically insufficient to detect locoregional disease due to the high false-positivity, most likely resulting from radiation-induced oesophagitis after nCRT. This is especially evident in patients who had cCR (and negative preoperative PET-CT) but still developed distant recurrence early after surgery.

For oesophageal cancer, MRD detection using ctDNA is still under investigation. In other cancers, ctDNA has been used to diagnose actionable mutations and detect targeted therapy resistance[11,17,23]. In the present study, personalized ctDNA analyses using a tumour-informed assay were used, which had a high sensitivity for detecting MRD. In the exploratory analysis, ctDNA was used as a diagnostic modality that reflected the status of systemic disease. The results indicated that ctDNA positivity at CREs was associated with an increased risk of systemic recurrence, regardless of whether the CREs detection using bite-on-bite biopsies and EUS-FNA were negative or positive. This finding is significant and provides a basis for the use of ctDNA in future organ-preserving strategies. ctDNA MRD detection may predict distant metastases earlier and even in patients who are suitable for active surveillance, additional systemic treatments may be considered in those who have detectable ctDNA.

Another question that needs to be considered in an organ-preserving strategy is whether delayed surgery has an impact on prognosis. The retrospective DICE study[24] demonstrated that prolonged interval between nCRT and surgery was associated with increased postoperative mortality rate and poorer survival. On the contrary, a recently published article showed that prolonged time to surgery in histologically proven residual disease after nCRT did not negatively affect survival[25]. However, the above studies aimed to assess the impact of delayed intervention on survival for all patients after nCRT and surgery, and results of the DICE study are likely influenced by selection bias due to inclusion of patients who underwent salvage surgery for recurrent disease after initially intended definitive CRT. The core of organ-preserving strategy is active surveillance for patients with cCR and postponed surgery after recurrence under frequent monitoring. The organ-preserving strategy for patients with cCR has been evaluated by SANO trial[5], in which postponed surgery in patients with active surveillance did not result in inferior survival and did not increase surgical risks, supporting its feasibility in patients with cCR after nCRT.

This study had some limitations. Neoadjuvant treatments are rapidly changing, especially the addition of immunotherapy[26]. Whether the data obtained from nCRT can be directly applied to patients with chemo/radio/immunotherapy remains unclear. Accurate evaluation of lymph nodes with EUS-FNA is still a challenge; some lymph nodes are small, some are difficult to puncture after treatment, or their location may not be readily accessible. Expertise in performing EUS-FNA in these difficult situations may not be universally available. Finally, ctDNA analysis was exploratory. The study was not designed using ctDNA as an outcome measure and longer follow-up is necessary to fully understand the prognostic value of ctDNA, particularly concerning distant relapse and overall survival.

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Meeting presentations

Results of this trial have partially been presented at ASCO Breakthrough, Yokohama, August 2024 (https://doi.org/10.1200/JCO.2024.42.23_suppl.196).

Disclosure

X.G. has received a personal research grant from the Nijbakker-Morra foundation. The other authors declare no other conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The authors confirm that the data supporting the findings of this study are available from the corresponding author, upon reasonable request.

Author contributions

Yang Yang (Data curation, Formal analysis, Methodology, Project administration, Writing—original draft, Writing—review & editing), Zhichao Liu (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Ian Wong (Data curation), Xing Gao (Data curation), Hong Zhang (Investigation), Jun Liu (Investigation), Ben M. Eyck (Methodology), Jinchen Shao (Investigation), Yu-Chen Han (Investigation), Berend J. van der Wilk (Methodology), Yinkai Chao (Project administration), Simon Law (Project administration, Writing—review & editing), Bas P.L. Wijnhoven (Project administration, Supervision, Writing—review & editing), J. Jan B. van Lanschot (Conceptualization, Project administration, Supervision, Writing—review & editing), and Zhigang Li (Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing—review & editing)

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