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LETTER TO THE EDITOR

Gastro-oesophageal junction: to FLOT or to CROSS?

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Introduction

For resectable adenocarcinoma (AC) of the gastro-oesophageal junction (GEJ), several treatment options are available including: perioperative chemotherapy and neoadjuvant chemoradiotherapy (nCRT) [1]. The superiority of these modalities compared to surgery alone was established in the randomized MAGIC (perioperative epirubicin, cisplatin plus fluorouracil), FFCD 9703 (perioperative; cisplatin plus fluorouracil) and CROSS (5 weekly cycles of carboplatin, paclitaxel and concurrent 41 Gy radiotherapy) trials [2–4]. MAGIC and FFCD 9703 contained both GEJ and gastric AC, while the CROSS trial included GEJ and oesophageal AC or squamous tumours. The heterogeneous inclusion criteria in these trials hampers the interpretation of finding the optimal modality, perioperative or nCRT, for GEJ tumours. Therefore, in clinical practice, the two modalities are used based on local preferences. Recently, the randomized FLOT-4 study published in *The Lancet*, compared an anthracycline based perioperative triplet regimen (ECF/ECX: epirubicin, cisplatin plus fluorouracil or capecitabine) to a docetaxel based perioperative triplet (FLOT: fluorouracil plus leucovorin, oxaliplatin and docetaxel) for patients with resectable GEJ or gastric AC [5]. FLOT significantly reduced mortality compared to ECF/ECX, hazard ratio (HR)=0.77 95% confidence interval (CI)=0.63–0.94, with a median overall survival (OS) of 50 months in the FLOT group vs. 35 in the ECF/ECX group. FLOT is thus a new treatment option for patients with resectable GEJ or gastric AC. However, if FLOT is preferred for GEJ tumours compared to nCRT according to the CROSS protocol is unknown. There are no direct comparisons available between the two strategies and the primary endpoint (OS) of the ESOPEC trial (NCT02509286) comparing CROSS with FLOT will not be available before 2023. Therefore, we conducted an exploratory network meta-analysis (NMA) to indirectly compare these regimens. The outcome of our NMA can help guide clinical care before a large randomized study has been conducted.

Material and methods

Literature search

PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for eligible randomized controlled trials up to May 2019. The search strategy consisted of medical subject headings (MeSH) and text words for gastric cancer and oesophageal cancer (see Supplementary material for full search strategy). Moreover, the abstracts from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meetings were searched up to May 2019.

Study selection

Eligibility criteria consisted of the following:

1. Prospective phase III randomized controlled trials with an intention-to-treat (ITT) population of ≥100 patients based on the combined sample size of both arms.
2. Investigating perioperative or neoadjuvant chemo(radio)-therapy for oesophageal or GEJ AC.
3. The ITT population should not include ≥75% gastric or squamous cell carcinoma (SCC) tumours.

Data extraction

HRs with 95% credible intervals (95% CrIs) were extracted for OS to calculate the logHR and standard error based on ITT study populations. When reported, oesophageal AC and GEJ subgroup HRs for OS were also extracted.

Statistical analysis

A random effects NMA was performed to compare multiple treatment modalities in one model and to perform an indirect comparison of CROSS with FLOT [6]. The NMA was

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conducted in the Bayesian framework using the GeMTC-standalone version (https://gemtc.drugis.org/signin.html), based on the GeMTC R-package [7]. The Bayesian model was used to incorporate the conditional probability of the direct estimates into the model. The number of burn-in iterations was set at 5.000 and the inference iterations at 20,000. To assess a correct posterior distribution, the potential scale reduction factor would be kept below 1.05 and the density plots would provide a smooth regular shape. Run lengths were extended if this was not the case and the Markov chains had not converged. Direct and indirect treatment effects were combined into a single effect size, and the relative effects between all treatments were calculated as combined HRs with 95% CrIs. Outcomes were deemed significant at an α-level of 0.05.

Subgroup analysis and node-split models

A subgroup analysis was performed for reported HRs for oesophageal AC and GEJ tumours. If trials reported the two locations separately, a combined HR was calculated in a fixed effect meta-analysis in Review Manager version 5.3. Node-split models were created to assess network consistency (between direct and indirect evidence).

Results

Network characteristics

Thirteen RCTs were included with a total number of 4983 patients (Figure 1, PRISMA flowchart and Supplementary Table 1). Five nodes were created in the network based on compound similarity: neoadjuvant cisplatin/5-FU based CRT, CROSS regimen, perioperative or neoadjuvant cisplatin/5-FU, perioperative or neoadjuvant ECF/ECX, FLOT regimen and surgery alone.

Results of the random-effects NMA

FLOT reached a non-significant HR of 0.88 (95% CrI 0.46–1.62) compared to CROSS for OS in the random-effects model (Figure 2(A)). Moreover, we performed a sensitivity analysis based on the subgroup HRs extracted for AC of the oesophagus including the GEJ. All 13 studies provided the

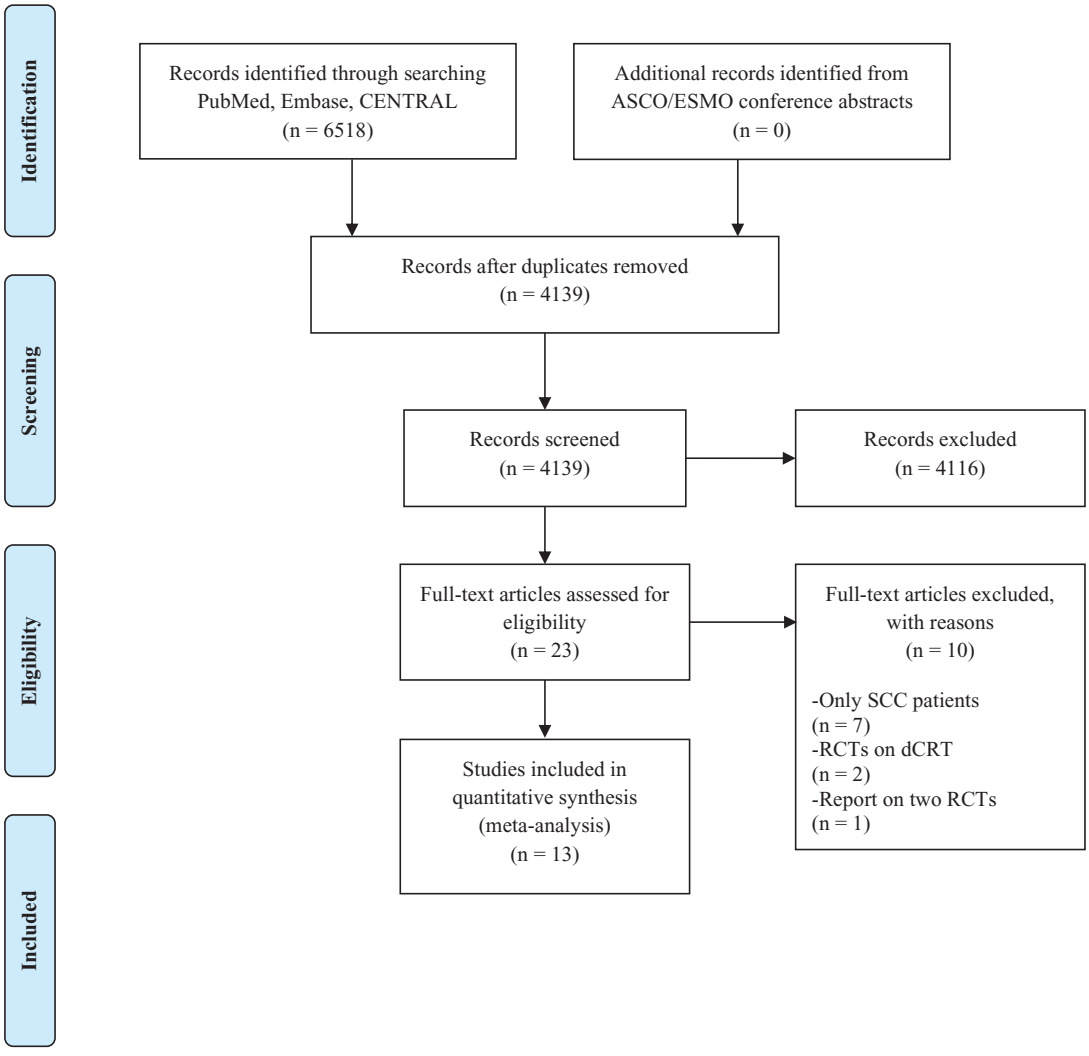

Figure 1. PRISMA flowchart of included studies. ASCO: American Society of Clinical Oncology; CENTRAL: Cochrane Central Register of Controlled Trials; dCRT: definitive chemoradiotherapy; ESMO: European Society for Medical Oncology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: randomized controlled trials; SCC: squamous cell carcinoma.

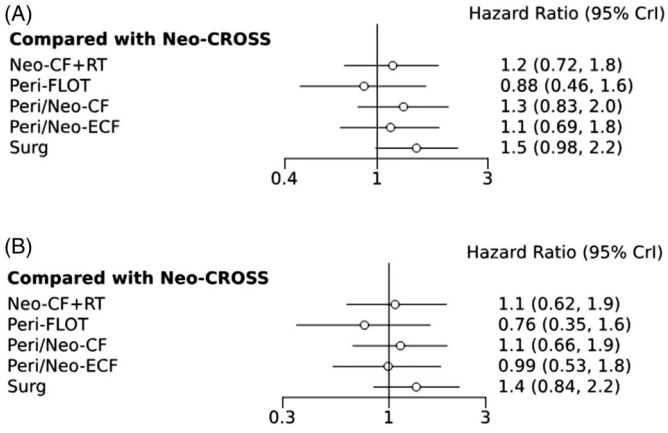

Figure 2. Random effects network meta-analysis for overall survival. (A) In total, 13 studies were included with mixed inclusion criteria: $N = 6$ (oesophageal adeno and squamous cell carcinoma), $N = 5$ (oesophageal adeno and gastric cancer), $N = 3$ (oesophageal adenocarcinoma). (B) Based on the reported hazard ratios (HR) for EAC and GEJ tumours, a subgroup analysis was performed. An HR > 1 indicates it is in favour of CROSS; if the HR < 1, the HR is not in favour of CROSS but of the comparator. The following regimens were included: Neo-CF + RT (neoadjuvant cisplatin with a fluoropyrimidine and radiotherapy) one study also added etoposide to this regimen [8], Neo-CROSS (carboplatin with paclitaxel and radiotherapy), Peri/Neo-CF (perioperative or neoadjuvant cisplatin with a fluoropyrimidine), Peri/Neo-ECF (perioperative or neoadjuvant epirubicin, cisplatin with a fluoropyrimidine), Peri-FLOT (perioperative docetaxel, oxaliplatin, 5-FU and leucovorin), Surg (surgery alone).

HRs needed for this analysis. In the sensitivity analysis, FLOT reached a non-significant HR of 0.76 (95% CrI 0.35–1.60) compared to CROSS (Figure 2(B)). All node split models for the main and subgroup analyses in the random effects NMAs were non-significant ($p > .05$) indicating comparable effect sizes between direct evidence and indirect estimates.

Discussion

Based on the available evidence synthesized in our exploratory NMA, no significant difference in OS was detected between FLOT and CROSS. A sensitivity analysis of only patients with AC of the oesophagus or GEJ did also not reach statistical significance. Therefore, until a well powered RCT proves otherwise GEJ tumours can be treated with CROSS or FLOT.

Other direct comparisons support the notion preoperative chemoradiotherapy and preoperative chemotherapy which are similar in terms of OS. The NeoRes trial randomized 181 patients with oesophageal cancer to preoperative cisplatin/5-FU with or without concurrent RT [9]. There was no statistically significant difference in terms of progression free and OS. Moreover, the subgroup analysis showed no sign of interaction between AC and SCC histology. The POET trial randomized 119 patients with Siewert type I–III tumours to preoperative cisplatin/5-FU or induction chemotherapy with sequential preoperative chemoradiotherapy [8]. The HR for OS was HR = 0.65 (95% CI 0.42–1.01 $p = .055$) in favour of the chemoradiotherapy arm. However, due to a non-significant p value it remains inconclusive about whether chemotherapy or chemoradiotherapy is preferred. The NeoRes and POET trial both used regimens which are no longer standard of care for GEJ tumours and were not adequately powered to detect a difference in OS. Therefore, the results of head to head comparisons with up to date regimens like the ESOPEC trial (CROSS vs. FLOT) are urgently awaited.

Our NMA has several limitations. First, several studies included mixed populations of gastric and oesophageal (SCC or AC). This could have influenced the results of our NMA. However, we used a random effects model and performed a subgroup analysis with only oesophageal AC patients showing a relatively consistent result. Second, the HRs we obtained had a wide confidence interval and the HR (0.76) in the sensitivity analysis for FLOT vs. CROSS was rather far away from the null. The wide intervals were due to the fact we used a random effects model and for some comparisons there was only one study available. Our results should therefore be interpreted with caution.

In conclusion, our exploratory NMA did not reveal any significant difference between the CROSS and FLOT regimen for oesophageal AC. Therefore, the two regimens can be used based on individual and patient preferences until a well powered RCT proves otherwise.

Author contributions

Tom van den Ende was involved in the literature search, creating the figures, study design, data collection, data analysis, data interpretation and writing.

Maarten Hulshof was involved in the interpretation of data and writing.

Mark van Berge Henegouwen was involved in the interpretation of data and writing.

Martijn van Oijen was involved in the design of the study, data analysis, data interpretation and writing.

Hanneke van Laarhoven was involved in the design of the study, data analysis, data interpretation and writing.

Disclosure statement

Drs. van den Ende has nothing to disclose. Dr. Hulshof has nothing to disclose. Dr. van Berge Henegouwen reports grants from Olympus and Stryker, personal fees from Mylan and Medtronic, outside the submitted work. Dr. van Oijen reports grants from Roche, Servier, Nordic, Merck, Amgen, outside the submitted work. Dr. van Laarhoven reports grants from Bristol-Myers Squibb, Bayer Schering Pharma, Celgene, Janssen-Cilag, Lilly, Nordic Group, Philips Healthcare, Roche, Merck Sharp and Dohme, personal fees from Lilly, AstraZeneca, Lilly, Nordic and Bristol-Myers Squibb, outside the submitted work.

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