Letter to the Editor

Standard or networked meta-analyses in assessing the best option for neo-adjuvant therapy in resectable oesophageal cancer: chemotherapy or chemo-radiotherapy?

Ewen A. Griffiths[1], Sandro Pasquali[2], Ravinder S. Vohra[3]

[1]Department of Upper Gastrointestinal Surgery, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [2]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Trent Oesophago-Gastric Unit, Nottingham University Hospitals NHS Foundation Trust, Nottingham, UK

Correspondence to: Ewen A. Griffiths, MD, FRCS. Consultant Upper GI Surgeon, Department of Upper Gastrointestinal Surgery, Area 6, 7th Floor, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK. Email: ewen.griffiths@uhb.nhs.uk.

Provenance: This is an invited article commissioned by Section Editor Dr. Hongcheng Zhu (Section Editor, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China).

Response to: Bedenne L, Le Malicot K, Drouillard A. Is it still time for meta-analyses in operable esophageal cancers, or rather for a change of paradigm? J Thorac Dis 2017;9:3594-7.

Submitted Sep 14, 2017. Accepted for publication Sep 18, 2017.
doi: 10.21037/jtd.2017.09.120
View this article at: http://dx.doi.org/10.21037/jtd.2017.09.120

We would like to thank Drs. Bedenne, Le Malicot and Drouillard for their commentary on our recently published networked meta-analysis (1). There is no worldwide agreement on the best perioperative oncological management of this disease so we are pleased this article has encouraged debate. It is notable the small amount of randomised evidence directly comparing CT with CRT as a neoadjuvant therapy in resectable oesophageal cancer (2,3).

Since the publication of most recent meta-analysis by Sjoquist *et al.* (4) four trials enrolling almost 1,100 patients have reported conflicting results (1). This meta-analysis only considered neoadjuvant therapies, but there is much debate about the efficacy of adjuvant therapies in resectable oesophago-gastric cancers. The diverse evidence in the literature allowed us an opportunity to compare adjuvant and neoadjuvant treatments with chemotherapy (CT), radiotherapy (RT), or chemoradiotherapy (CRT) using a novel 'network' meta-analysis. The advantage of this analysis over conventional direct meta-analysis is it allows the evaluation of treatments that have not been compared directly or indirectly by using a common reference that is part of all the RCTs, i.e., surgery alone (e.g., comparison of B versus C, using data from trials comparing A versus B and A versus C). Further, it ranks multiple treatments based simultaneously on their efficacy; and it pools together direct and indirect evidence within mixed comparisons improving the precision of estimates (5).

Different approaches to data interpretation are sometimes required to gain insight in to their clinical application and these analyses can be hypothesis-generating and inform the design of RCTs. For example, SUCRA (Surface Under the Cumulative RAnking) is Bayesian statistical approach interested in treatment efficacy rather than comparative statistics. It ranks different treatments rather than comparing. This is in contrast to frequentist statistics which uses hazard ratios (HR) to compare treatment effect.

We decided not to include Ychou *et al.* paper (6) as there were very few cases with oesophageal cancer included (decisional rule stated in our methods) (1). The omission of this study reduced number of patients by roughly 25, which will not have affected the power of our meta-analysis; which due to the networked approach is actually more complicated issue which is best accounted for by heterogeneity rather than simply the number of patients included.

Considering the available evidence, we were not able to draw conclusions on best neoadjuvant approach and recommend completing the several CT *vs.* CRT trial using contemporary RT techniques and latest chemotherapeutic drugs. The available evidence suggests CRT significantly

Table 1 Phase III trials comparing chemotherapy with chemoradiotherapy in the neo-adjuvant setting in oesophageal cancer which are currently recruiting

Study name, reference	Country	Tumour type	CT regimen	CRT regimen	Start date	Completion date	Target No.
NEOadjuvant Trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study (Neo-AEGIS) (9)	Ireland/ UK/ Denmark	Adeno	MAGIC regimen of 3 cycles of epirubicin, cisplatin and 5 fluorouracil/capecitabine	CROSS regimen of carboplatin and paclitaxel with RT 41.4 Gy/23 fractions	Aug 2012	Jan 2024	366
NEXT JCOG1109 (8)	Japan	SCC	CF (cisplatin plus 5-fluorouracil) or DCF (docetaxel, cisplatin plus 5-fluorouracil)	CF (cisplatin plus 5-fluorouracil) with 41.4 Gy RT	Nov 2012	Feb 2019	501
ESOPEC study (10)	Germany	Adeno	Peri-operative FLOT regimen chemotherapy (4 cycles pre and post)	CROSS regimen	Mar 2016	Jun 2023	438

CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

increases the pathCR response rate and this may confer a survival advantage; but not always (3,7). In other studies, there was the cost of an increased peri-operative morbidity and mortality, which offsets the survival gains (2).

Clearly, better designed pragmatic randomised trial evidence is required comparing these two neoadjuvant techniques in oesophageal cancer. Fortunately, three further high quality trials are currently recruiting patients (8-10) (*Table 1*). Although these will take time to be recruited and be published, it is hoped that they will clarify whether the increased rates of pathCR and potential survival gains from CRT are worth the risks of toxicity and potential peri-operative morbidity and mortality.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Pasquali S, Yim G, Vohra RS, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Ann Surg 2017;265:481-91.
2. Hamilton E, Vohra RS, Griffiths EA. What is the best neoadjuvant regimen prior to oesophagectomy: chemotherapy or chemoradiotherapy? Int J Surg 2014;12:196-9.
3. Klevebro F, Alexandersson von Döbeln G, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol 2016;27:660-7.
4. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-92.
5. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ 2013;346:f2914.
6. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
7. Favi F, Bollschweiler E, Berlth F, et al. Neoadjuvant chemotherapy or chemoradiation for patients with advanced adenocarcinoma of the oesophagus? A propensity score-matched study. Eur J Surg Oncol 2017;43:1572-80.
8. Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin

Oncol 2013;43:752-5.
9. Reynolds JV, Preston SR, O'Neill B, et al. ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC Cancer 2017;17:401.
10. Hoeppner J, Lordick F, Brunner T, et al. ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286). BMC Cancer 2016;16:503.

Cite this article as: Griffiths EA, Pasquali S, Vohra RS. Standard or networked meta-analyses in assessing the best option for neo-adjuvant therapy in resectable oesophageal cancer: chemotherapy or chemo-radiotherapy? J Thorac Dis 2017;9(10):E957-E959. doi: 10.21037/jtd.2017.09.120

