Letter to the Editor

The role of neoadjuvant chemoradiotherapy in multimodality treatment of esophageal or gastroesophageal junction cancer

Fredrik Klevebro, Magnus Nilsson

Division of Surgery, Department of Clinical Science Intervention and Technology (CLINTEC), Karolinska Institutet and Center for Upper Gastrointestinal Cancer, Karolinska University Hospital, Stockholm, Sweden

Correspondence to: Fredrik Klevebro. Division of Surgery, Department of Clinical Science Intervention and Technology (CLINTEC), Karolinska Institutet and Center for Upper Gastrointestinal Cancer, Karolinska University Hospital, Stockholm, Sweden. Email: fredrik.klevebro@ki.se.

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The issues raised by Stiles and Altorki in the editorial on our trial NeoRes are important and deserve in depth discussion and further study (1). We agree with Stiles and Altorki that there is currently no scientific basis at all for considering neoadjuvant chemoradiotherapy to be in any way superior to chemotherapy alone and as they point out there is some evidence that the addition of radiation increases postoperative morbidity and mortality without adding a long-term survival benefit for esophageal adenocarcinomas. Esophageal cancer is still a relatively rare condition, at least in Western populations, and it is difficult and expensive to perform large prospective studies. The scientific evidence for combination therapies is based on relatively small and heterogeneous RCTs. Furthermore there is evidence suggesting that the generalization of the results from trials to all patients have led to an overtreatment of unfit, co-morbid patients with perioperative oncological therapy (2) as the patients who are included in the trials are not representative of the average patient. Future studies need to focus on patient selection based on ability to tolerate treatment, frailty and tumor phenotype, enabling a finer granularity in the tailoring of treatment to individual patients.

An important point is that adenocarcinomas and squamous cell carcinomas of the esophagus are not the same diseases and should be treated as separate entities. Definitive chemoradiotherapy for squamous cell carcinomas is promising and should be further investigated in prospective trials. Two ongoing trials investigate the value of esophagectomy in patients with clinical complete response to nCRT, and have the potential to change practice (3,4). A problem with the study designs is however the poor accuracy, so far shown, in clinical complete response assessment. A study with randomisation of patients with squamous cell carcinoma, to CROSS-type nCRT and subsequent surgery *vs.* definitive chemoradiotherapy with surveillance and salvage surgery in clinically evident incomplete responders or in locally recurrent disease might be a better approach. This type of study is currently discussed in our research network.

Concerning adenocarcinomas the current question is to determine which combination therapy to recommend to each individual patient. A weakness of the NeoRes trial is that the chemotherapy regimen used in both arms was 5-FU and cisplatin, which is no longer the gold standard regimen. Several ongoing trials will increase the knowledge about perioperative treatment of esophageal and junctional adenocarcinomas. The Neo-AEGIS trial randomizes esophageal and junctional tumors to nCRT according to CROSS, or perioperative-chemotherapy according to the MAGIC-regimen (5) and recently the protocol has pragmatically been amended to allow the FLOT regimen in the chemotherapy arm. The TOPGEAR trial compares ECF treatment according to the MAGIC-

regimen or perioperative ECF treatment with the addition of preoperative chemoradiotherapy in gastric or junctional cancer (6). However, as pointed out by the authors the results of the FLOT trial showed superior tumor regression compared to the MAGIC-regimen, making it the most promising nCT regimen to date (7). The ESOPEC trial randomizes patients to FLOT or CROSS, currently the two combination treatments with the best efficacy in esophageal and junctional adenocarcinoma treatment (8). Another limitation of the NeoRes trial is that the primary outcome was tumor regression grade in the surgical specimen and not overall survival. nCRT has been repeatedly shown to increase the tumor regression grade and reduce R1 resections compared to nCT but the effect has not been translated to increased survival (1,9,10). Future trials should make sample size calculations based on overall survival as the primary outcome.

The rationale for adding radiotherapy to neoadjuvant chemotherapy in esophageal cancer treatment has not been scientifically proven. In the context of radical two-field esophagectomy, the primary tumor is treated twice, first with chemoradiotherapy and then with surgical resection, without any high grade evidence that it leads to a reduced risk of local recurrence or improved survival compared to nCT. It is possible that nCRT can benefit patients with bulky primary tumors or bulky nodal disease to reduce the risk of local recurrence, while perioperative or neoadjuvant chemotherapy, with its more intense systemic antitumor effects on occult metastatic disease, may be better for all other adenocarcinomas?

Radiation oncologists and surgeons can improve their cooperation when planning the radiation fields and the surgical resection. Maybe the neoadjuvant radiotherapy should focus on the lymph nodes that run a high risk of not being resected during the esophagectomy? Surgery and radiotherapy are both means of achieving local tumor control. Does very radical surgery combined with nCRT really make sense? Alternative roads to explore in future research should be to investigate limited radicality surgery, e.g., transhiatal esophagectomy in combination with nCRT, and compare with high radicality surgery with complete two-field lymphadenectomy and perioperative chemotherapy for systemic antitumor effect.

We can only agree with the conclusions made by our colleagues Stiles and Altorki. Based on today's evidence nCRT should perhaps be used for squamous cell carcinomas mainly and only for adenocarcinomas where R0 resection might be difficult or the risk of residual involved nodes is high. For all other adenocarcinomas nCT in combination with minimally invasive esophagectomy could be the treatment of choice.

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Footnote

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

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