

# Is it still time for meta-analyses in operable esophageal cancers, or rather for a change of paradigm?

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Since the eighties, several generally small and powerless trials compared surgery alone with surgery preceded or followed by radiotherapy (RT), chemotherapy (CT) or radiochemotherapy (CRT) in esophageal cancer. Since the years 2000, there have been many meta-analyses, the last one published in 2011 (1). Although only two new trials on the subject have been released since that time, a tenth meta-analysis was published in March 2017, subtitled “network meta-analysis” (2). What did it add to our knowledge? The conclusions of Sjoquist *et al.* were: (I) neoadjuvant chemoradiotherapy followed by surgery is superior to surgery alone [hazard ratio (HR) 0.78;  $P < 0.0001$ ] both in squamous cell cancers (HR 0.80;  $P = 0.004$ ) and adenocarcinomas (HR 0.75;  $P = 0.02$ ); (II) neoadjuvant CT followed by surgery is superior to surgery alone (HR 0.87;  $P = 0.005$ ); (III) the benefit of neoadjuvant CT seems limited to adenocarcinomas (HR 0.83;  $P = 0.01$ ); (IV) combining two trials (3,4), a direct comparison in adenocarcinomas of neoadjuvant CRT and CT resulted in a non-significant advantage of neoadjuvant CRT over CT [HR 0.77 (95 CI: 0.53–1.12)]; and (V) an indirect comparison in squamous cell cancers gave a borderline advantage to CRT (HR 0.88;  $P = 0.07$ ). The authors stated that “a clear advantage of neoadjuvant CRT over CT had not been established”.

The number of patients concerned by the meta-analysis by Pasquali *et al.* is greater (6,072 *vs.* 4,188), mainly because were included trials of adjuvant CRT and adjuvant CT,

which had been considered inefficient in randomized trials since the 90s (5). Actually, adjuvant CT (2 trials, 447 patients) and adjuvant RT (2 trials, 563 patients) do not improve the prognosis when compared with surgery alone. Generally speaking, adjuvant treatment shows no advantage (HR 0.87;  $P = 0.3$ ), although any neoadjuvant treatment versus surgery alone is significantly beneficial (HR 0.83;  $P < 0.001$ ). A randomized trial of adjuvant versus neoadjuvant CT had already led to this conclusion (6).

Pasquali *et al.* confirm the superiority of neoadjuvant CRT over surgery alone (HR 0.77;  $P < 0.001$ ), both in squamous cell carcinomas (HR 0.82;  $P = 0.003$ ) and adenocarcinomas (HR 0.76;  $P = 0.013$ ). However, concerning neoadjuvant CT, their results are contrary to those of Sjoquist *et al.*: the advantage over surgery alone is borderline significant overall (HR 0.89;  $P = 0.051$ ), and moreover is significant for squamous cell cancers (HR 0.89;  $P = 0.041$ ) but not for adenocarcinomas (HR 0.93;  $P = 0.48$ ). This result may be due to the fact that, although 10 trials were analyzed by Pasquali *et al.* versus 9 by Sjoquist *et al.*, there were fewer patients taken into account (1,960 *vs.* 1,981); particularly, the study FFCD 9703 by Ychou *et al.* was not considered because it had included stomach cancers along with cardiac and esophageal cancers (7). However, the study population could be split, so Sjoquist *et al.* had deleted the patients with primary stomach cancer. As the FFCD 9703 study was clearly in favor of neoadjuvant CT (HR 0.69;  $P = 0.02$ , with a

14% improvement of 5-year survival), its omission reduced the power of the present study.

The comparison between neoadjuvant CRT and CT concerned 3 trials (375 patients) versus 2 trials (191 patients) in Sjoquist's meta-analysis, resulting in the absence of advantage of CRT over CT. This is not surprising, as the added study found similar 3-year survival with the two treatments: 49% *vs.* 47% ( $P=0.77$ ) (8).

Consequently, concerning the results of the classical meta-analysis, we can consider that the study by Pasquali *et al.* does not add anything to our previous knowledge. Although the authors claim that a network meta-analysis, based on the assumed transitivity of the results, made possible a powerful comparison of neoadjuvant CRT and CT, we find puzzling and apparently contradictory results about this issue: the SUCRA values (Surface Under the Cumulative Ranking), "which equals 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst". So when considering all the neoadjuvant and adjuvant treatments, neoadjuvant CT ranked first (0.76), followed by neoadjuvant CRT (0.74), although in the next paragraph neoadjuvant CRT ranked first with a SUCRA value of 0.97, followed by neoadjuvant CT with 0.51. Moreover, after having written that subgroup analysis was not feasible for adenocarcinomas, the authors give a ranking of the treatments for these tumors: neoadjuvant CRT, SUCRA analysis 0.88, then neoadjuvant CT, SUCRA analysis 0.24. Equally confusing are the results of the network meta-analysis (*Figure 3* of the article): 21 comparisons were done without adjustment; as stated in the text, the only significant advantage over surgery alone was for neoadjuvant CRT (HR 0.77; 95% CI: 0.68–0.87), but when we look at the comparison of neoadjuvant CRT-surgery versus neoadjuvant RT-surgery, the HR is 1.04 (0.59–1.56), leading to consider that neoadjuvant RT is not different from neoadjuvant CRT. However, a meta-analysis (9) on individual data of 1,147 patients had concluded that there was no significant advantage of neoadjuvant RT over surgery alone (HR 0.89;  $P=0.062$ ). So, should we use again neoadjuvant RT, simpler and less toxic than CRT? Several other comparisons between adjuvant or neoadjuvant treatments result in a HR near to 1, which could lead to reconsider dramatically perioperative treatment of esophageal cancer.

But is it really the issue? The fact is that neoadjuvant CT or RT provide few pathological complete responses (pCR), between 2% and 10% (2,8,10–12), although neoadjuvant CRT produces between 16% and 43% pCR, usually around

30% (2,8,13–16). These 30% pCR are embedded in the 50% or more clinical complete responses (cCR) (17–19). Unfortunately, at the present time it is impossible to diagnose with accuracy the pCRs among the cCRs (20).

However, several non-randomized studies in Asia, Europe and America suggest that salvage surgery in case of operable loco-regional recurrence (i.e., non T4) allows the same R0 resection rate and 5-year survival as systematic surgery after neoadjuvant CRT (21,22). In the latter study, prognosis was better after salvage surgery than after planned surgery in case of partial or bad response (22), although the non-responders to CRT resected in the randomized FFCD 9102 trial (77/111, 69%) had a similar survival as the 259 responders, who were randomized between surgery and exclusive RCT, without difference in survival (23).

The present issue in esophageal cancer is thus to avoid unnecessary surgery, not only for pathologic complete responders, but also for those who will develop metastases as first recurrence. Actually, if the primary treatment is chemo radiation, about a third of all operable esophageal cancer patients will avoid surgery (18). This should close the debate about neo-adjuvant CRT or CT (or even RT).

European academic societies already recommend neoadjuvant CRT in locally advanced epidermoid cancer, and consider that in case of cCR, systematic surgery or surveillance with salvage surgery are equivalent options (24,25). However, this statement should be validated by the FFCD-driven PRODIGE 32-ESOSTRATE international randomized trial, which compares, in case of cCR after CRT, immediate surgery versus surveillance with salvage surgery, in adenocarcinomas and epidermoid cancers. The validation—or not—of this strategy is one of the main issues with this deadly disease.

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## Footnote

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

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