Editorial

The NeoRes trial: questioning the benefit of radiation therapy as part of neoadjuvant therapy for esophageal adenocarcinoma

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

Comment on: 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.

Submitted Aug 10, 2017. Accepted for publication Aug 21, 2017.
doi: 10.21037/jtd.2017.08.146
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.146

The "optimal" multimodality treatment for locally advanced esophageal cancer has seemingly been defined by the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial, with proponents arguing that neoadjuvant chemoradiation is the standard of care (1). However, sometimes lost in the enthusiasm over the excellent outcomes reported in this trial, is that CROSS is solely a comparison of neoadjuvant chemoradiation followed by surgery versus surgery alone. The CROSS trial cannot be used to suggest that neoadjuvant chemoradiation is superior to neoadjuvant chemotherapy alone followed by surgery. The NeoRes (Neoadjuvant Chemotherapy Versus Radiochemotherapy for Cancer of the Esophagus or Cardia) trial published by Klevebro *et al.* offers a better evaluation of these two strategies (2). The study randomized 181 patients at multiple institutions in Sweden and Norway with esophageal squamous cell carcinoma or adenocarcinoma to either three cycles of chemotherapy (nCT: cisplatin and fluorouracil) followed by surgery or to the same chemotherapy with concomitant radiation (nCRT: 40 Gy) with the second and third cycles followed by surgery. Not surprisingly, nCRT patients showed improved pathologic response to neoadjuvant therapy, with a 28% rate of complete pathologic response (CPR) and a 65% rate of negative lymph nodes. This compared favorably with the 9% CPR rate and a 38% rate of negative nodes following nCT. However, these indicators of local tumor response did not translate to improved survival. In an intention-to-treat analysis, the 3-year overall survival was 49% in the nCT arm and 47% in the nCRT arm (P=0.77). Three-year progression-free survival was 44% in both treatment arms. The lack of benefit of radiation was similar to what was previously reported in a randomized trial of 75 patients published by Burmeister *et al.* (3), which demonstrated a 3-year overall survival of 49% following nCT compared to 52% following nCRT (P=0.97). However, a third randomized trial by Stahl *et al.* (4), the POET trial (Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial) that included 126 patients suggested a strong trend towards a benefit of nCRT compared to nCT, with 3-year survivals of 47% with nCRT compared to 28% with nCT (P=0.07). Both the Burmeister and Stahl trials also showed higher rates of CPR and of nodal downstaging with nCRT, similar to the NeoRes results.

How should one reconcile these conflicting results and consider the importance of tumor pathologic response? First and foremost, it should be noted that radiation is a local therapy only (although admittedly in rare instances there may be abscopal immune effects). Conceptually, it is not clear why adding one local therapy to another (surgery) would improve survival, assuming that an appropriate surgical operation is performed. Admittedly, esophagectomy is perhaps one of the most challenging operations thoracic surgeons or surgical oncologists perform. But with an appropriate transthoracic operation, particularly with an en

bloc dissection of the esophagus and posterior mediastinal lymphatics and peri-esophageal tissue, excellent local control can be obtained surgically. Indeed, the differences in surgical quality may explain the differences noted between the Stahl and the Klevebro and Burmeister trials, in which only the nCT arm in the Stahl trial is a survival outlier. In the POET trial, only 47% of patients receiving nCT had transthoracic esophagectomy, compared to 90% and 100% in the Klevebro and Burmeister trials respectively. In subgroup analysis of randomized trial data (5), patients with moderate nodal metastatic burden treated by transthoracic esophagectomy had superior survival compared to those treated by transhiatal esophagectomy (5-year DFS of 64% *vs.* 23%, P=0.02). We expect that with the infrequent use of transthoracic resections, such as in the Stahl trial, radiation may indeed improve local control and survival. However, our group, along with surgeons from MD Anderson and McGill University, have published data showing that with transthoracic en bloc esophagectomy, nCRT provides no survival advantage over nCT for patients with cT3N1 esophageal adenocarcinoma (6). We would argue that en bloc esophagectomy with complete mediastinal exoneration provides unparalleled local disease control and is the surgical equivalent of a complete pathologic response. In such cases any benefit of radiation may be limited. The real question then becomes that of systemic response, which obviously depends upon the chemotherapy given. One compelling argument in favor of nCT alone is that it may be better tolerated than nCRT, allowing patients to receive the full course of intended chemotherapy cycles. This is illustrated in the NeoRes trial in which 85% of nCT patients received all three chemotherapy cycles compared to just 74% of nCRT patients.

Similarly and related to treatment tolerance, another compelling argument in favor of nCT over nCRT as an induction strategy is the potential adverse consequences of radiation therapy in this often debilitated patient population. Trial data and a large meta-analysis have suggested an increase in postoperative complications following nCRT compared to nCT (7-9). Although the NeoRes trial did not show a difference in the overall rate of complications between patients undergoing nCT or nCRT, it is compelling to note that the severity of complications was markedly higher in nCRT patients (10). And although the differences in perioperative mortality were not statistically different, the increase in 90-day mortality from 3% with nCT to 6% with nCRT (P=0.24) is troubling and is consistent with the increase in perioperative mortality seen in the POET trial, from 3.8% to 10% respectively (P=0.26). If one is intellectually prepared to accept the non-statistically significant difference in overall survival in that trial, then one must also accept the non-statistically significant difference in perioperative mortality. Klevebro *et al.* appropriately emphasize the marked increase in non-cancer related deaths the first year after nCRT in their trial. Indeed, 46% of the 24 nCRT patients who died in the first year died of non-cancer related causes. So with the added cost of radiation therapy, there would seem to be added morbidity and mortality that may not be apparent just by looking at 30-day outcomes.

One final important facet of the NeoRes trial merits discussion. Although not powered to detect differences in outcome based upon tumor histology, Klevebro *et al.* suggest that any potential benefit of nCRT is really only driven by patients with squamous cell carcinoma. Indeed, in patients with adenocarcinoma, the survival curves actually favor nCT (although not statistically significant). We have seen a similar differential effect in our own institutional data. Even in the CROSS trial (11), it is apparent that the benefit of nCRT is much more impressive in patients with squamous cell carcinoma than in those with adenocarcinoma (HR 0.46; P=0.004 *vs.* HR 0.75; P=0.059). The most recent meta-analysis of the two strategies also suggested only modest differences in hazard ratios comparing nCT versus nCRT to surgery alone (HR 0.83 and HR 0.75, respectively) in adenocarcinoma patients (12).

In conclusion, the NeoRes results published by Klevebro *et al.* add more weight to the concept that radiation therapy may not be required as part of neoadjuvant therapy for locally advanced esophageal cancer and may even potentially be counterproductive. This is particularly true of patients with esophageal adenocarcinoma in whom an en bloc transthoracic esophagectomy is planned. The recent results reported with the use of neoadjuvant FLOT (neoFLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) add strength to the argument of chemotherapy alone (13). Schulz *et al.* reported a 20% rate of CPR with this regimen in gastric and GEJ tumors, along with another 20% of patients demonstrating near complete histological remission with <10% residual tumor. These results are similar to CPR rates reported with nCRT in adenocarcinoma patients. As reported this past year, FLOT improved OS compared to the MAGIC trial regimen (median 50 *vs.* 35 months, P=0.012) and was associated with no significant increase in overall perioperative complications or mortality (14). Clearly the FLOT regimen is very

promising. The ESOPEC (Perioperative Chemotherapy Compared to Neoadjuvant Chemoradiation in Patients with Adenocarcinoma of the Esophagus) trial meant to compare FLOT to nCRT using the CROSS regimen is currently accruing patients and should more clearly define the role of nCT *vs.* nCRT in patients with adenocarcinoma (15). Along with more trials, more translational research needs to be performed to determine which patients may have radiosensitive tumors and to determine which patients may be most at risk for adverse events secondary to radiation therapy. Gene expression profiling and radiogenomic approaches have already begun to define those populations.

Until then, a tailored approach to neoadjuvant therapy seems appropriate. For patients with squamous cell carcinoma recommended for surgery, we prefer nCRT followed by en bloc three-field McKeown esophagectomy. For patients with lower esophageal or gastroesophageal junction adenocarcinoma, I favor nCT followed by en bloc Ivor Lewis esophagectomy. This is particularly true for tumors involving the upper stomach, in which the gastric conduit may receive significant radiation. Either surgical approach can be performed well minimally invasively. For adenocarcinoma patients with bulky tumors or nodal disease in which it is thought that an R0 surgical resection may be difficult to achieve or for those who are thought to be too frail for transthoracic esophagectomy, nCRT followed by transhiatal esophagectomy should be considered.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Stiles reports financial relationship of his spouse with Pfizer and receipt of consulting fees from Merck. Dr. Altorki has no conflicts of interest to declare.

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Cite this article as: Stiles BM, Altorki NK. The NeoRes trial: questioning the benefit of radiation therapy as part of neoadjuvant therapy for esophageal adenocarcinoma. J Thorac Dis 2017;9(10):3465-3468. doi:10.21037/jtd.2017.08.146

