Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus: the (NEOCRTEC5010) trial—a timely and welcome clinical trial from the Far East

Toni Lerut

Department of Thoracic Surgery, University Hospital Leuven, Leuven, Belgium

Correspondence to: Toni Lerut, MD, PhD. Kortrijksestraat 191, 3010 Leuven, Belgium. Email: toni.lerut@kuleuven.be.


doi: 10.21037/jtd.2018.10.39
View this article at: http://dx.doi.org/10.21037/jtd.2018.10.39

Each year world-wide approximately 400,000 cancers of the esophagus are registered. Half of them are occurring in China being squamous cell cancer (SCC) in over 90% the patients. This is in contrast with the Western experience where adenocarcinoma is the predominant cancer type.

Since the publication of the CROSS trial (1) the standard of care for locally advanced cancer of the esophagus and gastro esophageal junction today consists in induction chemotherapy +/- radiotherapy followed by surgery provided the patient is medically fit.

However, in this trial the fraction of SCC patients was relatively small. Therefore, a more specific trial dealing SCC would clearly be of interest.

Given the very high incidence of SCC in the Far East, in particular in China, many centers are dealing with very high volumes of SCC.

Units performing more than 1,000 esophagectomies/year are not an exception. These high-volume centers have developed an exceptional clinical experience with outstanding results in terms of postoperative complications and mortality.

Perhaps and precisely because of the outstanding surgical outcomes primary surgery has remained until today the standard of care in most centers in China.

The recent published NEOCRTEC5010 trial (2), a well-designed large scale randomized controlled trial exclusively dealing with SCC therefore may be seen as a landmark trial.

Yang and colleagues compare the results of primary surgery versus induction chemo-radiotherapy (NCRT) followed by surgery for squamous cell carcinoma of the esophagus. It is a phase III multicentric, randomized open label controlled clinical trial dealing with a large series of 451 consecutive patients.

The conclusion of the trial is that NCRT plus surgery improves survival over surgery alone in patients with locally advanced SCC with acceptable and manageable side effects.

Complete response was 43.2%, R0 resection rate was 98.4% versus 91.2% Median survival was 101 versus 66.5 months and disease-free survival 100.1 versus 41.7 months. All these results are significant. Mortality was 2.2% and 0.4%, respectively.

The NEOCRTEC5010 trial confirms the results obtained in the CROSS trial that induction therapy is superior to primary surgery both for adenocarcinoma as well as and more specifically for the SCC fraction.

Compared to the CROSS trial these results are quite spectacular the median overall survival after induction chemo-radiation being 81.6 months and after surgery 21.1 months in the report on the long term follow up of the CROSS trial (3).

However, comparing trials is a difficult exercise and some aspects require a closer analysis.

In the NEOCRTEC5010, the inclusion criteria have been very selective.
Age limit was 70 years with a median age of 56 in the CRT and 58 years in the surgery group. In the CROSS trial, age limit was 75 years and the median age was 60 years.

In the NEOCRTEC5010 trial patients had to have a Karnofsky performance score of ≥90 which is equal to full activity whereas the CROSS trial used the WHO 0–1 scale thus also including patients who were symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work).

In other words, both age and performance status are a bias that may favor the outcome in the Chinese trial.

On the other hand, clinical T3N0 were excluded in the Chinese trial but not in the CROSS trial which in its turn may negatively affect the outcomes in the Chinese trial.

In this context it is worth to notice that both in the uni- and multivariable analysis no significant difference was seen between cN0 and cN+. This is unusual since N+ is reported to result in significantly lower outcome as compared to cN0 (stage II vs. stage III) (4).

Most likely this is related to the exclusion of cT3N0. Thus the only N0 group being respectively 34 and 27 cT4N0 tumors with an obvious higher tumor burden than the cT3N0 and also being a relatively small group questioning adequate statistical analysis.

Most impressive is the overall 5-year survival both after induction: 101 months as well after primary surgery: 66.5 months compared to 81.6 and 21.1 months respectively in the CROSS trial.

The explanation for this can be related to the bias caused by age and performance advantage in the Chinese trial but one can speculate this being without a significant influence.

It may well be related to the induction scheme using vinorelbine—cisplatinum combination versus the carboplatin paclitaxel combination.

Perhaps a Chinese trial comparing the CROSS regimen with the NEOCRTEC5010 regimen could shed some light on the which regimen is most effective.

Whether the addition of the lymphadenectomy in the superior mediastinal compartment including the recurrent nerves nodes is beneficial is still controversial.

Studies from the East in general claim a survival benefit when performing an extended 2 field (and/or 3 field lymphadenectomy) in SCC after primary surgery (5).

Studies from the West, predominantly dealing with adenocarcinoma, question the advantage of extended lymphadenectomy in particular after neoadjuvant chemoradiotherapy while other studies claim a benefit (6,7).

The results of the actual study seem to endorse the potential advantage of extended 2-field lymphadenectomy in SCC in both the surgery as well as in the induction arm given the superior results.

The final question is whether despite the high pCR and resulting downstaging induction therapy is of real benefit in overall survival.

Although the difference in overall survival is significant, the significance is moderate (P=0.025).

The follow up is relatively short, i.e., a median follow up of 41 and 34.6 months respectively with too many patients being censored after 2 years follow up indicating that important changes still can occur.

In conclusion, this is the first large scale trial on comparing induction chemo-radiotherapy plus surgery versus surgery alone in SCC coming from China the country with the highest incidence of this tumor type in the world. The trial is well designed and is to be considered as a landmark trial.

The results seem to favor the induction arm both for overall and disease-free survival and thus confirming the data obtained in the smaller scale SCC patients in the CROSS trial.

However before conclusive statements can be made a longer follow up is mandatory to confirm the consistency of the results.
with the actual findings. The longer term results are therefore eagerly awaited for.

**Acknowledgements**

The author thanks J Moons, Data Manager, Clinical Research Coordinator; and L Depypere, Joint Clinical head from the Department of Thoracic Surgery, University Hospital Leuven, Belgium for their valuable contribution in preparing this Editorial.

**Footnote**

**Conflicts of Interest:** The author has no conflicts of interest to declare.

**References**


**Cite this article as:** Lerut T. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus: the (NEOCRTEC5010) trial—a timely and welcome clinical trial from the Far East. J Thorac Dis 2018;10(Suppl 33):S4162-S4164. doi: 10.21037/jtd.2018.10.39