The role of neoadjuvant chemoradiotherapy vs chemotherapy in cancer of oesophagus

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Abstract
Oesophageal malignancies are accounted as the eighth most common malignancy across the globe and the sixth leading cause of cancer-related deaths. The mortality to incidence ratio noted to be 0.88. The momentum towards neoadjuvant and adjuvant treatments is therefore understandable. Neoadjuvant radiochemotherapy (nRCT) has emerged as a standard of care in most parts of the world and we review the strength of evidence in favour of the same viz a viz neoadjuvant chemotherapy.

Introduction
Oesophageal malignancies are accounted as the eighth most common malignancy across the globe and the sixth leading cause of cancer-related deaths. The mortality to incidence ratio noted to be 0.88 [1]. Besides the difference in the histological entities, oesophageal malignancies have seen a difference in the incidence across the globe with varied patterns of incidence in the West and the East with squamous cell carcinoma (SCC) being the most common pathology in Asia and adenocarcinoma in North America and Europe. Surgery remains the mainstay of definitive treatment. The anatomical location of oesophagus in close proximity to many critical organs with an absence of serosal lining makes spread by direct extension quite common which in turn makes R0 resection difficult for many patients. The rich submucosal network of lymphatics also makes lymph node metastases quite common. Therefore it is understandable that historically potential resectability has been about 30 to 40% only with 30-50% rates of positive margins leading to five-year survival rates of just 15 to 20% [2-4]. The momentum towards neoadjuvant and adjuvant treatments is therefore understandable. Neoadjuvant radiochemotherapy (nRCT) has emerged as a standard of care in most parts of the world and we review the strength of evidence in favour of the same viz a viz neoadjuvant chemotherapy.

Neoadjuvant radiochemotherapy
In recent decades, several studies have investigated the benefit of nRCT for oesophageal cancer. Randomised controlled trials comparing nRCT followed by surgery with surgery alone, were initiated in first in 1986 and 1989 [5,6]. After nRCT plus surgery, Apinop et al. reported pathologically complete response (pCR) rate of 27% and Urba et al. reported it as 28% not significantly improving median survival and three-year overall survival between both groups. However, both studies were not powered for detecting small changes in overall survival.

Following this, two sufficiently powered trials were performed [7,8] Walsh et al. randomised 113 patients with oesophageal adenocarcinoma between nRCT (40 Gy, administered in 15 fractions over a three-week period with two courses of chemotherapy in weeks 1 and 6 (Cisplatin with fluorouracil) plus surgery versus surgery alone [7]. Over a median follow-up of 10 months. A significant improvement in median overall survival (16 vs. 11 months, p<0.01) and three-year overall survival (32% vs. 6%, p<0.01) was reported for patients receiving nRCT. Burmeister et al. [8] reported randomised results of 256 patients with adenocarcinoma or squamous cell ca randomised between nRCT (one cycle of cisplatin and fluorouracil with concurrent 35 Gy in 15 fractions) followed by surgery versus surgery alone. A low pCR rate of 16% was observed and 80% R0 resections were observed in in patients receiving nCRT viz a viz 59% of patients after surgery alone (p<0.001). Median overall survival was not significantly different between both groups (22.2 vs. 19.3 months, p=0.570). In 2010, Lv et al. [8] reported randomised data on 238 patients with squamous cell carcinoma and reported R0 resection rate of 97.4% as compared with 80% in surgery alone group. They reported a significantly better median overall survival (53 vs. 36 months, p<0.005) and five-year overall survival (43.5% vs. 33.8%, p ¼ 0.0402) in favour of the nRCT plus surgery group. Lee et al. reported randomised data of 101 patients with squamous cell carcinoma. Between nRCT (two cycles of cisplatin and fluorouracil with concurrent 45.6 Gy radiotherapy in 38 fractions) followed by surgery versus surgery alone [9]. The R0 resection rate after nRCT compared to primary surgery was 100% vs. 87.5% (p=0.037) with 43% pCR rates. However, the median overall survival was comparable (28.2 vs. 27.3 months). An important stride in nRCT was taken with reporting of the the Dutch CROSS trial [10,11]. Between 2004 and 2008, 366 patients with locally advanced squamous cell- or adenocarcinoma of the oesophagus or oesophagogastric junction were randomised between...
nRCT (five weekly cycles of carbopepitan and paclitaxel and 41.4 Gy radiotherapy in 23 fractions) followed by surgery versus surgery alone. R0 resections were more common in nRCT arm versus surgery alone arm (92% vs. 69%, p<0.001) with 29% pCR rates. The median overall survival was better in the nCRT group (48.6 vs. 24 months, p<0.003) [11]. The five-year overall survival in nRCT arm was 47% compared to 33% in the surgery alone arm with similar postoperative mortality rates (4% vs. 4%, p=0.700). Unlike the dutch CROSS trial that included patients with locally advanced cancer of esophagus, the French FFCD 9901 trial included 195 early stage (stages I or II) oesophageal cancer patients with squamous cell carcinoma or adenocarcinoma. They were randomised between nRCT (two cycles of cisplatin and fluorouracil with concurrent 45 Gy radiotherapy in 25 fractions) plus surgery versus surgery alone. R0 resection rates were comparable between both groups (93.8% vs. 92.1%, p=0.749) with pCR rates of 35.8% with significantly higher postoperative deaths occurred in the nRCT plus surgery arm (11.1% vs. 3.4%, p=0.049). A possible explanation for this is the fact that most centers included were not high-volume [12]. No increased mortality rate was reported in the CROSS study where carboplatin with paclitaxel was used instead of cisplatin with fluorouracil (radiation schedules were comparable). The number of patients proceeding to surgery in FFCD study were just 86% compared to 92% in CROSS trial. The median overall survival in the FFCD 9901 trial was not significantly different between the nRCT plus surgery group and the surgery alone group (31.8 vs. 41.2, p=0.940).

Many of the above studies were not sufficiently powered to show significant advantage of nRCT followed by surgery over surgery alone, resulting in contradictory results. Sjoquist et al. reported their meta-analysis to assess the benefit of nRCT for operable oesophageal cancer patients [13]. Thirteen studies included compared chemoradiotherapy plus surgery versus surgery alone with a total of 1932 patients. Most studies used a neoadjuvant regimen of cisplatin and fluorouracil with concurrent 20-50.4 Gy radiotherapy. They reported a pooled hazard ratio (HR) for all-cause mortality of 0.78 (95%CI 0.70-0.88, p<0.0001), which is the equivalent of a two-year overall survival benefit of 8.7% when patients are treated with nRCT followed by surgery compared to surgery alone. The HR for the overall indirect comparison of all-cause mortality for nRCT versus neoadjuvant chemotherapy (nCT) was 0.88 (0.76-1.01; p=0.07). This technically means that there is no significant difference between two approaches of nRCT or nCT.

A recent meta-analysis by Jing et al. from China reported comparison between nRCT and nCT approaches by including only randomised trials. Three eligible randomized controlled trials were included with a total of 375 patients (189 nRCT, 186 nCT). The HR for the overall indirect comparison of all-cause mortality for nRCT versus nCT was 0.75 (0.40-1.41; p=0.001). Once again the fact that there is no significant difference between the two approaches of nRCT and nCT brings us to our next section.

**Neoadjuvant chemotherapy vs radiochemotherapy**

Oncologists commonly advise peri-operative or neoadjuvant chemotherapy (nCT) basing the recommendation on the MAGIC trial [14]. The MAGIC trial reported results on 503 patients with adenocarcinoma of the distal oesophagus, oesophagogastric junction or stomach. Patients were randomised between perioperative chemotherapy (three preoperative and three postoperative cycles of epirubicin, cisplatin and fluorouracil) plus surgery versus surgery alone. The median survival after a median follow-up period of 48 months was significantly better in the perioperative chemotherapy group than in the surgery alone group (23.5 vs. 19.5 months, p<0.009). However since 74% of patients included in the MAGIC trial had adenocarcinoma of the stomach, it is not equitable to extrapolate these results to adenocarcinomas of the distal oesophagus or oesophagogastric junction. In 2002, Medical Research Council Oesophageal Cancer Working Group reported results of a randomised controlled trial [15] on 802 patients with resectable oesophageal squamous cell- or adenocarcinoma. Patients were randomised between nCT (two cycles of cisplatin and fluorouracil) followed by surgery versus surgery alone. After a median follow-up of 37.4 months, median survival was significantly better in the preoperative chemotherapy group than in the surgery alone group (16.8 vs. 13.3 months, p<0.004). R0 resections were achieved in 65% of patients in the nCT group and in 56% of patients in the surgery alone group with a pCR rate of 4% with nCT. Long term follow-up reported in 2009 reports an absolute benefit of 5% with nCT [16]. The results of RTOG 8911 trial [17] contradict results of OEO2 trial. In the RTOG 8911 trial, 440 patients with oesophageal squamous cell- or adenocarcinoma were randomised between perioperative chemotherapy (three preoperative cycles of cisplatin and fluorouracil and for responders two additional postoperative cycles of cisplatin and fluorouracil) followed by surgery versus surgery alone. After a median follow-up of 46.5 months, median overall survival was comparable between the perioperative chemotherapy group and the surgery alone group (14.9 vs.16.1 months, p=0.53). R0 resections were reported in 78% of patients undergoing surgery in the perioperative chemotherapy group and in 62% of patients in the surgery alone group with a pCR rate of 2.5% after a minimum of one cycle chemotherapy. The discrepancy in outcome between the OEO2 and RTOG 8911 trial may be explained by the fact that patients receiving chemotherapy in the RTOG 8911 trial were less likely to undergo surgery since 20% of patients in the perioperative group did not proceed to surgery in contrast with 4% in the surgery alone group. This rate was only 10% and 3% respectively in the perioperative chemotherapy and surgery alone group as reported in the OEO2 trial (vs. 3% in the surgery alone group).

Sjoquist et al. reported meta-analysis of pooled data of trials investigating neoadjuvant chemotherapy [13]. Ten studies with a total of 2062 patients comparing chemotherapy followed by surgery versus surgery alone were included. The MAGIC trial was excluded because there were just 26% patients with oesophageal or junctional cancer. Also, the operations performed were mostly gastrectomies. This meta-analysis reported a survival benefit for patients treated with preoperative chemotherapy of 5.1%. When comparing both treatment strategies only two studies directly comparing both neoadjuvant therapies were identified [18,19]. These studies were both underpowered for overall survival because just 75 and 119 patients were enrolled. Neither study reported a significant benefit for one of both neoadjuvant regimens by direct comparison. Both authors [18,19] concluded nRCT to be a better option than nCT. However with a total of 2220 patients, the pooled hazard ratio for all-cause mortality in the nRCT followed by surgery group was 0.88 (0.76-1.01, p=0.070) compared to the nCT group thus making nRCT and nCT statistically comparable neoadjuvant options with a criticism of inclusion of trials that themselves reported superior results with nRCT.

In 2019 Von Döbeln GA et al. [20] reported results of NeoRes I which is a randomized phase II trial comparing nRCT with nCT in the treatment of resectable cancer of the esophagus or gastroesophageal junction. Patients with biopsy-proven adenocarcinoma or squamous cell carcinoma, T1N1 or T2-N0-1 and M0-M1a were randomized to receive three 3-weekly cycles of cisplatin and fluorouracil with or without the addition of concurrent radiotherapy 40 Gy, 2 Gy/fraction.
5 days a week, followed by surgery. Primary endpoint was pCR rate in the primary tumor. Survival and recurrence patterns were evaluated as secondary endpoints. A total of 181 patients were enrolled. nRCT arm reported more pCR (28% vs. 9%). Five-year progression-free survival was 38.9% in the nRCT group versus 33.0% (P=0.82) in the nCT group and the five-year overall survival was 42.2% versus 39.6% (P=0.60) respectively. There were no differences in recurrence patterns between the treatment groups.

A systematic review by Jing et al. [21] published in 2019 only analysed three eligible randomized controlled trials that compared nRCT with nCT and included a total of 375 patients. They reported that nRCT results in higher pCR rate and higher R0 resection rates when compared with nCT without significantly affecting survival in resectable esophageal and junctional cancer. While the sample size seems to be small, the included studies are all RCTs, so the level of data and conclusions obtained is very high.

Therefore it is clear that nRCT produces larger pCR rates and R0 resections than nCT but the same doesn't translate into a more superior survival benefit. The most promising report of the dutch CROSS trial uses paclitaxel and carboplatin as concurrent chemotherapy regimen whereas most other studies use cisplatin and fluorouracil. For nCT the most promising results are from the FLOT study where they used docetaxel along with cisplatin and fluorouracil [22].

The proponent for nRCT allude to the superior pCR and R0 resection rates that are clinically encouraging whereas the proponents for nCT quote the statistical non-superiority of either approach and higher toxicity with nRCT.

It is possible that nRCT may increase treatment-related toxicity and postoperative complication rates. Stahl et al. [18] reported numerically higher in-hospital mortality by adding preoperative radiation therapy (two of 52 patients undergoing surgery [3.8%] vs five of 49 patients undergoing surgery [10.2%] in nCT and nRCT, respectively; P=0.26). The NeoRes 1 trial [20] reported no differences between the treatment arms in terms of frequency of postoperative complications, although complications appeared to be more severe in the nRCT arm. Fan et al. meta-analysis [23] showed an increase in perioperative mortality and postoperative complications when radiotherapy was utilized. Kumagai et al. [24] hypothesized that preoperative nCRT significantly increased postoperative mortality and treatment-related death in patients with ESCC, potentially explaining the lack of survival benefit despite better tumor response. They however concluded that there is no difference in toxicity overall between nRCT Vs nCT approach. Burmeister et al. [19] compared complication rates and showed no statistical difference between the two treatment modes (p=0.05). More treatment-related toxicity and postoperative complication rates in nRCT might be the reason for that a higher pCR and R0 resection rate cannot confer a survival advantage.

Therefore, in search for a scientific recourse to qualifying patients for nRCT in clinical practice perhaps we should strictly follow the patient related eligibility criteria laid down in the landmark trial like the dutch CROSS trial [11] to minimize the morbidity and maximize the benefit for our patients. The patient related criteria for eligible patients were aged 75 years or younger with adequate haematological, renal, hepatic, and pulmonary function; and a WHO performance score of 2 or better, without a past or present history of other malignancy. The main exclusion criteria were past or current history of malignancy other than the oesophageal malignancy, previous chemotherapy and/or radiotherapy, and weight loss of more than 10% of the original bodyweight.

Eelke et al. [25] published a comparison of outcomes on patients receiving Dutch CROSS protocol of nRCT outside the trial compared with the patients within the trial who received nRCT. They reported no statistically significant differences in adverse events (pulmonary, cardiac, or anastomotic complications) or survival between the comparison cohorts. Another report by de Heer et. [26] enrolled 161 patients with locally advanced EC (T1N1-3/T2-4aN0-3/M0) treated with the CROSS schedule followed by esophagectomy. There were two groups, group 1 met the CROSS criteria and the group 2 met the extended eligibility criteria, i.e. a tumor length greater than 8 cm, more than 10% weight loss, more than 2-4 cm extension in the stomach, celiac lymph node metastasis, and/or age over 75 years. The study assessed the differences in nRCT-associated toxicity, 90-day postoperative mortality. The prognostic factors for OS was assessed using Cox multivariate analysis. No difference was found in nRCT-associated toxicity (P=0.117), postoperative complications (P=0.783), and 90-day mortality (P=0.492). The OS differed significantly (P=0.004), with a median of 37.3 months for group 1 and 17.2 months for group 2. However the tumor related factors of pathologic N stage (P=0.023), pathologic T stage (P=0.043), and group 2 (P=0.008) were independent prognostic factors for OS. In another report by Von Döbeln GA et al. on patients of NeoRes1 trial authors reported results of a cardiac stress test on a stationary bicycle and a spirometry that were performed before and after neoadjuvant treatment and 1 to 2 years later after surgery provided that the cancer had not recurred. While they reported impairment in pulmonary function measured as vital capacity and forced expiratory volume in 1 second and a decrease in exercise capacity after neoadjuvant treatment and 1 to 2 years later after surgery. They did not report any differences between nRCT or nCT patients.

It is therefore clear that nRCT as per CROSS protocol can be reasonably extrapolated to practice without much perceived increase in morbidity to the patients and that there is no clear evidence of higher post-operative morbidity with nRCT except for the possibility of squamous cell carcinoma.

**Future directions**

The controversy on the optimal treatment strategies for operable oesophageal carcinoma patients will remain until well-designed randomised trials are performed which directly compare nRCT according to the CROSS regimen with neoadjuvant chemotherapy according to MAGIC or FLOT. Currently, two ongoing randomised trials are addressing this issue [27,28]. The German ESOPEC trial (NCT02590286) aims to randomise 438 patients with locally advanced oesophageal or junctional adenocarcinoma between nRCT plus surgery (CROSS regimen) and perioperative FLOT chemotherapy plus surgery [27]. The Irish NEOAEGIS trial (NCT01726452) aims to randomise 540 patients with locally advanced oesophageal or junctional adenocarcinoma between CROSS and MAGIC or FLOT chemotherapy, followed by surgery [28]. These trials will likely provide evidence for the optimal neo adjuvant or peri-operative treatment in patients with carcinoma of the oesophagus. The Japanese Next trial [29] (ICOgg 1109, UMIN000009482) aims to randomise 501 patients with mostly locally advanced oesophageal squamous cell carcinoma into three neoadjuvant regimens plus surgery: 1) neoadjuvant chemotherapy with cisplatin and fluorouracil (similar to OEO2 and RTOG 8911), 2) neoadjuvant chemotherapy with fluorouracil, cisplatin and docetaxel (similar to FLOT), and 3) nCRT with cisplatin, fluorouracil and 41.4 Gy radiotherapy in 23 fractions, 5 fractions a week similar to FFCD 9901).
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