Review Article

Definitive chemoradiotherapy

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Abstract: Definitive chemoradiotherapy (dCRT) is reflecting a treatment standard in oesophageal cancer. For irresectable localised tumours and for inoperable patients, dCRT can change the treatment intent from palliative to curative. In patients with squamous cell carcinoma (SCC), in particular in those of cervical location, dCRT is a proper alternative for treatment that may include radical surgery. Patients with localised locoregional recurrence after primary surgery can survive for long-term after salvage CRT.

Keywords: Definitive chemoradiotherapy (dCRT); oesophageal cancer

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Introduction

In 1992 the RTOG 85-01 trial established definitive chemoradiotherapy (dCRT) as standard for non-operative therapy of localised oesophageal carcinoma (1). This prospective, randomized phase III study evaluated the efficacy of four courses of cisplatin and 5-fluorouracil (5-FU) combined with 50 Gy of radiation compared to 64 Gy of radiotherapy alone in patients with squamous cell carcinoma (SCC, n=106) or adenocarcinoma (AC, n=15) of the oesophagus. Surgery was reserved only for recurrences or complications. The study showed a significant survival advantage in patients with the combined modality. Median survival was 12.5 months for those receiving chemoradiotherapy versus 8.9 months with radiotherapy alone and 5-year survival reached 26% compared to 0%.

Subsequent randomized studies have confirmed these findings of dCRT with survival rates of 35–40% at 2 years and about 20% at 5 years (2-4). More recent investigations were able to identify prognostic factors for long term survival. A population-based study from the Netherlands showed survival rates at 2 years of 29% and 17% in patients with SCC and AC and histology represented an independent prognostic factor in multivariate analysis (5). In patients with oesophageal SCC from Taiwan the 3-year survival dropped down from 42% in stage I to 25% and 16% in stage II and III, respectively (6). A research group from the US defined a nomogram that was predicting long term survival after dCRT in patients with mostly oesophageal AC (7) and initial T-category as well as response to dCRT (evaluated by positron emission tomography and biopsies) reflected important factors for scoring prognosis. The same investigators looked at 141 patients who obtained initial clinical complete response to dCRT (8) and 75% of the patients had AC. At a median follow-up of 22 months 55% experienced disease recurrence. By multivariate analysis treatment failure correlated with non-Caucasian ethnicity, node positive disease, and advanced T-category (e.g., cT3-4).

Although not proven by large studies it appears that patients with SCC of the proximal oesophagus, so called cervical cancers, have a particular poor prognosis (9). Definitive CRT with modern radiation techniques and increased doses above 60 Gy reached 3-year survival rates of about 25% and distant recurrences were prevalent (10).

Patients with oesophageal cancer and in particular those with SCC often present with comorbidities which increase the risk for postoperative complications. It is

not well documented which percentage of patients with localised oesophageal cancer will never undergo surgery due to increased operative risk. However, from those who were judged as candidates for primary surgery, the rate of in hospital mortality reached about 5% in experienced European centers (11). From that it was important to compare potentially curative treatment approaches with and without surgical resection.

Definitive CRT versus primary surgery in localised oesophageal cancer

Researchers from Japan (12) compared dCRT to primary surgery in patients with early stage SCC (clinical stage T1bN0M0). Overall 173 patients were included into this retrospective, unicentric analysis. Like in other studies, understaging was a problem and tumor stage pT1b was confirmed after surgery in 53% of the patients, only. In the dCRT group radiation doses from 50 to 60 Gy were applied in combination with cisplatin and 5-FU. Treatment related mortality was zero in this experienced center. The survival rate at 5 years was higher after surgery (77.7% *vs.* 68.6%), but this difference was not statistically significant (P=0.12). However, progression free survival was significantly improved in patients with surgery, which was caused by improved local tumor control.

A group from the UK (13) reported on a prospective, non-randomized comparison of patients with SCC or AC of the oesophagus treated with dCRT (n=173) or primary surgery (n=126). Significantly more patients in the dCRT group had SCC and locally advanced tumors of stage III and IVA (74% *vs.* 38%). Nevertheless, the overall survival (OS) did not differ between groups [hazard ratio (HR) =0.83, 95% confidence interval (CI), 0.62–1.12].

A small trial from China (14) randomized eighty patients to dCRT (50-60 Gy combined with two cycles of cisplatin and 5-FU) or surgery (two-field lymphadenectomy), but informed consent was obtained after recruitment to the trial. Two third of the patients had locally advanced SCC according to endoscopic ultrasound. Despite this fact, the rate of complete resection was high (86%). Postoperative mortality reached 6.8%. There was a trend in favour of improved disease free survival after 5 years in patients with dCRT (47% *vs.* 25%, P=0.07), and also long-term OS was numerically increased in this treatment group (5 year survival 50% *vs.* 29%; P=0.15). The advantage in favour of dCRT was more pronounced in patients with clinically involved lymph nodes (5-year survival rate 47.4% *vs.* 11.8%, P=0.06). However, it remains unclear, why im contrast to other studies local tumor control was improved with dCRT compared to surgery (50% *vs.* 36%).

In 2012 Pöttgen *et al.* performed a meta-analysis including 6 studies that compared definitive radio(chemo) therapy with surgery and 3 out of these 6 studies included primary surgery without preoperative therapy (15). The majority of patients had oesophageal SCC. There was no difference in OS between treatment modalities (HR =0.98, P=0.84). However, more patients died from their oesophageal tumour after radiotherapy (P=0.07), whereas significantly more patients died from treatment related causes after surgery (P=0.001). Local tumour progression was predominant in patients with radio(chemo)therapy (P<0.001) and distant metastases were more often observed in patients with surgery (P=0.06). The authors stated that dCRT is equivalent to surgery (with and without preoperative) therapy in locally advanced SCC of the oesophagus.

Definitive CRT versus preoperative chemo/ chemoradiotherapy

Two European phase III studies compared dCRT with preoperative CRT and surgery. A German study (2) randomized 172 patients with locally advanced SCC to induction chemotherapy followed by chemoradiotherapy (40 Gy) and surgery or induction chemotherapy followed by dCRT (at least 65 Gy). The authors reported equivalent OS with a 2-year survival rate of 39.9% *vs.* 35.4% (P=0.007 for equivalence at a difference of 15%) and an updated long term survival at 10 years of 19.2% *vs.* 12.2% (logrank, P=0.36) (16). The addition of surgery significantly increased treatment-related mortality (12.8% *vs.* 3.5%, P=0.03). However, local tumour control favoured trimodal therapy as freedom from local tumour progression was significantly worse after dCRT (at 2 years 40.7% *vs.* 63.3%, P=0.003). A second study, the French FFCD 9102 trial, recruited 444 patients with resectable oesophageal cancer of predominantly SCC subtype (3). After induction CRT (46 Gy in 23 fraction/4.5 weeks or 30 Gy in 10 fraction/4 weeks combined with cisplatin and 5-FU), 259 patients with responding tumours were randomized to surgery or further chemoradiation (to a total radiation dose of 66 Gy in 33 fractions or 45 Gy in 15 fractions). Again, survival times were comparable between treatment groups (2-year survival rate 39.8% *vs.* 33.6% (P=0.03 for non-inferiority at a difference below 10%). The rate of

early death was significantly higher with surgery (3-month mortality 9.3% *vs.* 0.8%) as was local tumour control (at 2 years 66.4% *vs.* 57.0%). The results of these European studies prompted guidelines to recommend dCRT as a valid option in the curative therapy of locally advanced SCC of the oesophagus (17,18).

A recent meta-analysis of the Cochrane database (19) analysed 7 studies with 1,114 participants with regard to benefits and harms of non-surgical therapy compared to oesophagectomy. Four studies with 602 patients covered the comparison of dCRT with surgery (with and without adjunctive therapy) in operable patients with oesophageal cancer, and most of the patients had SCC. There was no difference in long-term mortality between dCRT and surgery (HR =0.88, 95% CI, 0.76–1.03). Moreover, there was no difference in long-term cancer recurrence between non-surgical and surgical treatment. The authors stated that dCRT appears to be at least equivalent to surgery in short-term and long-term survival only in patients with SCC, whereas there is more uncertainty in patients with AC. Of note, the authors emphasize that the evidence was low or very low because the included studies were small and had errors in study design. Moreover, the reader of this meta-analysis wonders whether it can be helpful to collectively analyse such heterogeneous studies that investigated surgery alone, preoperative CRT and postoperative RT or CRT.

Which radiotherapy dose to apply for definitive CRT?

The optimal radiotherapy dose and fractionation is still a matter of debate. Long term (5 years) locoregional control rates after radiotherapy and dCRT vary between 32% and 75%. In most trials, improved locoregional tumor control was associated to higher total radiation doses (4,20,21), concurrent chemotherapy (22), lower tumor volume (21), and SCC histology (22). However, improved locoregional tumor control after higher radiation doses at least in locally advanced oesophageal cancer seems not to translate into an improved OS (4,20).

Randomized data on radiation dose escalation is available only from the INT 0123 trial (4). Patients (n=208) with predominantly locally advanced oesophageal cancer (87% squamous cell carinomas) were randomly assigned to receive 50.4 Gy in 28 fractions in 5.5 weeks or 64.8 Gy in 36 fraction in 7 weeks. Chemotherapy consisting of four cycles of cisplatin and 5-FU was identical in both arms of the trial. After a 2-year follow-up locoregional control was moderately improved by 4% to 56% (not significant) in the high dose group, but a trend towards a worse OS was observed (31% *vs.* 40%). During radiotherapy 11 deaths were observed in the high dose arm *vs.* 2 deaths in the lower dose arm (P<0.01). Of note, 7 out of 11 deaths during radiotherapy in the high dose arm occurred at total doses ≤50.4 Gy and could thus not be a result of the higher prescribed radiation dose. During further follow-up 13 deaths not related to the index cancer were observed in the high dose arm *vs.* 3 in the lower dose arm (P<0.01). Whereas the latter observation could be related to increased late radiation toxicity in the high dose arm, the relation of the former observation to high dose radiotherapy remains obscure. Consequently, the results of the INT 0123 are not conclusive and do not exclude a benefit from higher radiation doses than 50.4 Gy in conventional fractionation.

The FFCD 9102 trial (3) randomized oesophageal cancer patients responding to chemoradiation to undergo furher chemoradiation or surgical resection. Two different radiotherapy schedules were allowed in this trial: either 30 Gy in 10 fraction in 4 weeks (split course) followed by additional 15 Gy in 5 fractions (total dose 45 Gy) after a 2-week break for restaging and randomization, or 46 Gy in 23 fractions in 4.5 weeks followed by additional 20 Gy in 10 fractions (total dose 66 Gy) after a 1.5 weeks break for restaging and randomization. Chemotherapy consisted of an identical cisplatin and 5-FU regimen in both arms. Centers had to choose one radiotherapy regimen before treating the first patient and were obliged to stick to this regimen during the whole trial. The resulting two dose groups were well balanced for known risk factors except for significantly more AC (18%) treated in the low dose group compared to the high dose group (8%). Locoregional tumor control at 2 years was significantly better (P=0.002) at 66 Gy (77%) than at 45 Gy (56%). However, this gain in locoregional tumor control did not translate into a significantly improved OS predominantly due to a high distant failure rate.

In summary, it appears that a high distant failure rate and higher rates of deaths not related to the index cancer associated with higher radiation doses counteract a clinical meaningful benefit from higher doses of radiotherapy in locally advanced oesophageal cancer. As a result, most US and European cooperative groups consider 50 Gy in 25 fractions or 50.4 Gy in 28 fractions as the standard radiotherapy regimen for dCRT protocols (23,24). However the discussion on the optimal radiation dose is not closed. Investigators from Japan and China consider total doses of 59.4 to 66 Gy in 30–33 fractions as standard

radiotherapy (25,26). Modern radiation techniques like IMRT and VMAT using simultaneous integrated boost radiotherapy have been shown to considerably decrease the dose to critical organs like heart and lungs (27,28). Excellent results have been reported from a phase II trial (n=60) using these technologies to administer 66 Gy in 30 fractions in combination with 2 cycles of cisplatin and 5-FU (29). Randomized trials using modern radiation techniques and escalated doses are ongoing and will hopefully clarify this issue.

In cervical oesophageal cancer radiation induced late effects are generally less severe and consequently investigators from all parts of the world agree that higher radiation doses in the range of 60 to 70 Gy in 30–35 fractions should be administered (9).

Which chemotherapy to use for combined definitive CRT?

The RTOG 85-01 trial established two cycles of cisplatin and 5-FU combined with radiotherapy followed by another two cycles of chemotherapy alone for standard dCRT in oesophageal cancer. However, the toxicity of this treatment was relevant. In the study 20% of the patients had life threatening side effects and 2% died from treatment related toxicity (1). In a later RTOG-study (94-05, INT 0123) using the same regimen more than 70% of the patients developed side effects of grade 3 or higher (4). Upon these experiences, study groups investigated CRT with combinations other than cisplatin and 5-FU to decrease toxicity and to improve the compliance with therapy that may also improve treatment efficacy.

A French intergroup study (PRODGE 5/ACCORD17) performed a sequential phase II/III study comparing the probably less toxic chemotherapy schedule FOLFOX4 combined with 50 Gy of radiotherapy to the standard RTOG regimen (24). Of 267 patients were randomised into this study and six cycles of FOLFOX4 were applied, 3 of them concomitant to radiotherapy. Similar results were observed between treatment groups regarding clinical CR rate (44% *vs.* 43%), progression free and OS (median survival 20.2 *vs.* 17.5 months, survival rate at 3 years 19.9% *vs.* 26.9%, HR =0.94, P=0.70). Relative dose intensity of 5-FU and platinum was comparable in both treatment groups, as was percentage of patients with premature stop of chemotherapy and overall toxicity. However, less toxic deaths occurred in the FOLFOX4 group compared to dCRT with cisplatin and 5-FU (1% *vs.* 6%).

The so called CROSS-regimen (30) substituted cisplatin by weekly carboplatin and introduced weekly paclitaxel instead of 5-FU into combined preoperative CRT. Due to it's very good tolerability this regimen gained high acceptance in Europe and raised the interest in investigating taxane-based chemotherapy also in dCRT.

A propensity matched analysis of retrospective data was performed by investigators from China (31). Radiotherapy was applied with single doses of 1.8 to 2.0 Gy up to a total dose of 50.4–70 Gy. Two cycles of cisplatin and 5-FU (60 mg/m^2 day 1 and 300 mg/m^2 continuous infusion day 1–3 of each cycle) were compared to two cycles of cisplatin and docetaxel (80 and 60 mg/m^2, day 1). Comparing 156 *vs.* 131 patients with localised SCC the authors reported a significantly improved progression free and OS (P=0.009) in favour of the latter regimen, but it remains unclear whether results were driven by including a taxane into the experimental group or by the reduced dose of cisplatin and the unusual dose of 5-FU in the so called standard group of this analysis.

A group from the Netherlands reported on their experience with adapting the CROSS-regimen for dCRT (32). This retrospective study analysed patients with locally advanced oesophageal or junctional cancer who had received dCRT to a total dose of 46.8–70 Gy (and additional intraluminal brachytherapy in single patients) either combined with four cycles of cisplatin and 5-FU (RTOG 8501-regimen) (n=47) or with 5–6 weekly applications of carboplatin (AUC 2) and Paclitaxel (50 mg/m^2) (n=55). Patients with the standard regimen were more likely to have SCC (60% *vs.* 42%) and less often had kardio-pulmonal comorbidities (19% *vs.* 38%). The chance of completing planned dCRT was significantly higher in the carboplatin group (82% *vs.* 57%, P=0.01) and the treatment related mortality was numerically lower (1.8% *vs.* 4.3%) as was overall toxicity. Results of disease free and OS were comparable (cisplatin/FU: median OS 16.1 mo, carboplatin/paclitaxel: median OS 13.8 mo, P=0.97). From these results it appears that carboplatin/paclitaxel may reflect an alternative chemotherapy also in dCRT, although the evidence with this chemotherapy combination is somewhat lower in SCC than in AC of the oesophagus. A randomised comparison of standard dCRT and dCRT including weekly carboplatin/paclitaxel would be helpful to define the standard combination.

The UK National Cancer Research Institute Upper GI Clinical Studies Group investigated the role of adding the epidermal growth factor receptor (EGFR) inhibitor

cetuximab to dCRT (23) in resectable oesophageal cancer (AC, SCC, or undifferentiated carcinoma). Treatment consisted of induction chemotherapy (two cycles cisplatin and capecitabine) followed by dCRT (50 Gy combined with two cycles of cisplatin and capecitabine) with or without weekly cetuximab. The SCOPE1 study was terminated early after 258 patients had been recruited because the trial met predetermined criteria of futility. OS was significantly worse in the cetuximab group [2-year OS 41.3% *vs.* 56.0%, HR =1.45 (1.01–2.09), P=0.04] and subgroup analysis favoured dCRT alone particularly in patients with SCC. Problems with study compliance (19% *vs.* 8% of randomised patients never received radiotherapy) and with increased toxicity during combined dCRT including cetuximab which prevented patients from receiving the planned dose of radiotherapy (full dose applied in 78% *vs.* 90% of the patients) may have influenced the results. Clinical tumour stage, full-dose radiotherapy and cisplatin dose-intensity proved prognostic factors in multivariate analysis. So, EGFR-inhibition combined with dCRT cannot be recommended in unselected patients with oesophageal cancer.

Induction chemotherapy prior to dCRT

Despite its unproven value a couple of study groups used neoadjuvant or induction chemotherapy before definitive treatment (2,23). The rationale was that primary chemotherapy allows time for careful radiotherapy planning and that shrinkage of the tumour before dCRT appears to lead to better compliance with the treatment (33). Two prospective, randomized phase II trials investigated the role of induction chemotherapy prior to chemoradiotherapy and surgery. Yoon *et al.* from Korea randomized 97 patients with localized (stage II–IVA) SCC of the oesophagus (34). Preoperative chemoradiotherapy consisted of 46 Gy combined with oxaliplatin and the oral fluoropyrimidine S1. In the experimental arm patients were allocated to two cycles of induction chemotherapy with oxaliplatin and S1. The rate of pathologic complete response (pCR) was chosen as the primary endpoint. Treatment results between study groups were comparable with regard to toxicity, surgical complications, tumour regression, as well as progression free and OS (2-year OS 60.7% versus 63.7% with and without induction chemotherapy). Also the pCR rates of 23.4% *vs.* 38.0% (P value not stated) were obviously not statistically different. A US American group investigated induction chemotherapy before CRT and surgery in 124 patients with oesopago-gastric AC. Again pCR-rate was the primary endpoint. Chemoradiotherapy with a radiation dose of 50.4 Gy in combination with oxaliplatin and 5-FU was preceded or not by four cycles of oxaliplatin and 5-FU. The authors observed a trend for an improved local tumour response in favour of the group that received induction chemotherapy (pCR rate 25.9 *vs.* 12.7%, P=0.09). Toxicity of preoperative treatment, surgical morbidity and mortality as well as survival data were not different between treatment groups. From these trials it can be concluded that induction chemotherapy is feasible and does not increase toxicity of (preoperative) CRT. So, for practical issues it´s use appears an option instead of applying chemotherapy after dCRT like in the RTOG 85-01 standard, although a randomized comparison in dCRT of oesophageal cancer has not been performed, so far.

Definitive CRT for salvage treatment after radical surgery

Two retrospective Asian studies reported on the results with dCRT in patients with localised tumour recurrence after primary radical surgery. The Japanese study (35) included only patients with solitary lymph nodes metastasis, and 33/35 patients had SCC. Patients received a platinum-based chemotherapy (number of cycles not stated) combined with radiotherapy of 60 Gy. After a median follow-up of 33.5 months the calculated OS at 5 years was 39.2% and the tumour control within the radiation field reached 59.9% at 5 years. A study from China (36) treated 50 patients with SCC and local recurrence was observed at the anastomosis (n=7) or in lymph nodes at different sites. The radiation dose ranged from 50.4 to 64 Gy with a median dose of 60 Gy. Two cycles of concurrent chemotherapy with cisplatin and 5-FU or cisplatin and paclitaxel were applied. The follow-up was only 16 months and the authors reported a median survival of 13.3 months. The survival rate at 3 years was calculated for 14%.

From these retrospective studies we can conclude that salvage CRT is feasible in patients with localised recurrent oesophageal SCC after radical surgery and long-term survival is possible.

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Footnote

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