Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial).

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Background: The most effective multimodal approach for treatment of resectable locally advanced esophageal adenocarcinoma (EAC) is under debate. A prior ranking question is if neoadjuvant chemoradiation therapy or perioperative chemotherapy is superior. ESOPEC (NCT02509286) is a multicenter prospective randomized trial comparing neoadjuvant CROSS (41.4Gy plus carboplatin/paclitaxel) followed by surgery versus perioperative FLOT (5-FU/leucovorin/oxaliplatin/docetaxel) and surgery for the curative treatment of EAC. Methods: Patients with cT1 cN+ cM0 or cT2-4a cNany cM0 resectable EAC were eligible. The primary endpoint is overall survival (OS; 90% power; hazard ratio [HR] 0.645, 218 events needed; one sided significance level of 2.5%). Analysis is by intention-to-treat in all randomized patients. The effect of treatment on OS is estimated using Cox regression stratified by study site, and including N stage (N0, N+), and age as covariates. Results: Between Feb 2016 and Apr 2020, 438 patients from 25 sites in Germany were randomly assigned to two treatment groups (221 FLOT; 217 CROSS). Baseline characteristics (male sex 89.3%, median age 63 [range 30-86], cT3/4 80.5%; cN+ 79.7%) were well balanced between both arms. Neoadjuvant treatment was started in 403 patients (207 FLOT; 196 CROSS). Surgery was done in 371 patients (191 FLOT; 180 CROSS). R0 resection was achieved in 351 patients (180 FLOT; 171 CROSS). 90 days postsurgical mortality was 4.3% (3.2% FLOT; 5.6% CROSS). After a median follow up of 55 months, 218 patients had died (97 FLOT; 121 CROSS). Median OS was 66 (95% CI 36 – not estimable) months in the FLOT arm, and 37 (95% CI 28 – 43) months in the CROSS arm. The 3-year OS rates were 57.4% (95% CI 50.1 – 64.0%) for FLOT and 50.7% (95% CI 43.5 – 57.5%) for CROSS (HR 0.70, 95% CI 0.53–0.92, p=0.012). In 359 patients with available tumor regression status, pathological complete response was achieved in 35 (19.3%, 95% CI 13.9 – 25.9%) in FLOT and in 24 (13.5%, 95% CI 8.8 – 19.4%) in CROSS. Conclusions: Perioperative FLOT improves survival in resectable EAC compared to neoadjuvant CROSS. Funding: The trial was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), project number 264590883. Clinical trial information: NCT02509286. Research Sponsor: DFG.