The Initial Report of Local Control on RTOG 0436: A Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for Patients with Esophageal Cancer Treated without Surgery

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Purpose/Objective(s): RTOG 0436 is a randomized Ph III trial designed to evaluate the benefit of cetuximab added to the concurrent chemoradiation for patients undergoing non-operative management of esophageal carcinoma. While the primary endpoint was to evaluate overall survival, the impact on local control was an important secondary objective.

Materials/Methods: Pts with biopsy proven squamous cell or adenocarcinoma of the esophagus (T1N1M0; T2-4 Any N M0; Any T/N M1a) were randomized to weekly concurrent cisplatin (50 mg/m2), paclitaxel (25 mg/m2) & daily radiation 50.4 Gy/1.8 Gy fractions ± weekly cetuximab (400 mg/m2 day 1 then weekly 250 mg/m2). Patients were stratified by histology, tumor size (< 5 cm vs > 5cm) & the status of celiac lymph nodal involvement. Overall survival (OS) was the primary endpoint, with a planned accrual of 420 pts to detect an increase in 2-year OS from 41% to 53%; 80% power & 1-sided 0.025 alpha. Local failure (LF) was first assessed 6-8 weeks following tx with endoscopy and patients were determined to have a clinical complete response (cCR) or not. Biopsy confirmation of residual/recurrent disease was required. Following cCR, LF was defined as biopsy/endoscopy proven primary recurrence or surgery to the primary site. LF & OS were estimated with the Kaplan-Meier method & compared with stratified log-rank tests.

Results: The study accrued 344 pts from 2008-2013 & 328 were eligible. Based on interim analyses, the study stopped accruing adeno pts in 5/2012 & SCC pts in 1/2013. Pts were well matched for pretreatment characteristics: 80% with T3/4 disease, 66% N1, & 19% with celiac nodal involvement. Incidence of grade 3/4/5 treatment (tx) related AEs was 45%, 22%, 4% in Arm 1 (cetuximab) & 49%, 17%, 1% in Arm 2 (no cetuximab). A cCR rate of 56% was observed in Arm 1 vs 59% in Arm 2 (p=0.72). No differences were seen in cCR between tx arms for either histology. Median follow-up for all pts is 16.3 mos. The 12 and 24 mo LF (95% CI) for Arm 1 was 35% (28%, 44%) & 45% (36%, 54%) vs 42% (34%, 50%) & 49% (41%, 58%) for Arm 2 (p=0.41). The 12 & 24 mo OS rates for cCR pts were 79% & 60% vs 52% & 30% for those with residual disease [p<0.0001]. The 12 & 24 mo OS for Arm 1 is 64% (56%, 71%) & 45% (37%, 53%) vs 65% (57%, 72%) & 42% (35%, 50%) for Arm 2 (p=0.59).

Conclusions: The addition of cetuximab to concurrent chemoradiation did not improve OS. Similarly there was no difference between treatment arms in terms of local control. These Ph III results add to the growing body of literature that points to little benefit for unselected pts using current EGFR targeted agents and highlights the need for predictive biomarkers in the treatment of esophageal cancer.

Acknowledgment: Supported by RTOG CA21661 & CCOP CA3742 NCI grants and Bristol Myers Squibb.

Purpose/Objective(s): RT is known to relieve dysphagia of advanced oesophageal cancer, there is no data from randomised phase III trials determining response, toxicity, or role of palliative CRT. Aims 1) to establish effective and least toxic treatment for symptom relief of advanced OC 2) determine effects of common cancer treatments on QoL and end of life care 3) establish an evidence base for patient decision making regarding the optimal management for incurable OC.

Materials/Methods: 220 patients were randomised to receive a course of palliative RT [35 Gy in 15 fractions in Australia and New Zealand, (n=115) or 30 Gy in 10 fractions (n=105) in Canada and UK], or concomitant CRT with Cisplatin and 5FU (D1-4) (n=111). Dysphagia was measured using the Mellow score, toxicity using CTCAE v2, and QoL using EORTC QLQ30 and oesophagus module (OES-18). The primary end point was the proportion of patients with improved dysphagia as measured at week 9 and maintained until week 13.

Results: The patients receiving radiotherapy alone showed a dysphagia response (at any point) of 67.89% compared to chemotherapy response in 73.87% (p=0.343). There was increased gastro-intestinal toxicity in patients receiving CRT (nausea (p=0.0019) and vomiting (p=0.0072)). The median survival was 210 days for CRT and 203 days for RT alone. The baseline parameters of both groups were well matched at randomisation and although the results of the trial showed equally poor survival prognosis in both arms, there were some patients (n=21) still alive at 2 years post treatment.

Conclusions: CRT was associated with increased gastro-intestinal toxicity without any significant improvement in dysphagia response or median survival. Further analysis of QoL, toxicity and durable palliative response will be published. This multicentre trial reflects practice in several countries. RT alone remains an excellent tool for palliation of patients with advanced OC and should remain the standard of care.

Local Excision Versus Total Mesorectal Excision in Patients with Good Response After Neoadjuvant Radiochemotherapy for T2-T3 Low Rectal Cancer: Preliminary Results of the GRECCAR 2 Randomized Phase 3 Trial


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Purpose/Objective(s): To compare local excision (LE) and total mesorectal excision (TME) in patients with a good response after neoadjuvant radiochemotherapy for low rectal cancer.

Materials/Methods: Patients with T2T3 low rectal carcinoma, maximum size 4 cm and within 8 cm from anal verge received neoadjuvant radiochemotherapy. Good clinical responders (residual tumor ≤ 2 cm) were randomized between LE and TME. In the LE group, patients with a good pathologic response (ypT0-1) had surveillance, while those with a bad pathologic response (ypT2-3 or R1) had a complementary TME. Here we report the preliminary results in term of feasibility and tumor response.

Results: From 2007 to 2012, 195 patients were included in 15 french centres of the Group for Surgical Research on Rectal Cancer (GRECCAR). Radiochemotherapy consisted in 50 Gy / 2 Gy per fraction five days a week over a period of 5 weeks with concomitant chemotheraphy (capecitabine 1600 mg/m²/d five days a week). The rate of clinical response was 71% (115 of 162 patients included before treatment). Overall, 148 patients were randomized, three were excluded and 145 patients were analyzed: 74 in the LE group and 71 in the TME group. Compliance to surgery was higher in the LE than in the TME group (99% vs. 85%; p=0.002). In the LE group, 35% (26/74) had a complementary TME. The pathologic tumor response showed ypT0/40%, ypT1/21%, ypT2/32% and ypT3/7%. A good pathologic tumor response (ypT0-1) was more frequent in T2 than T3 tumors (69% vs. 51%; p=0.02). The rate of positive lymph nodes in good pathologic responders (ypT0-1) was very low compared to bad responders (ypT2-3): 0% vs. 15% ypN1 (CI95% = 0%-8.2%; p= 0.012).

Conclusions: This study showed a good compliance for de-escalation of treatment by using a 3-step strategy in patients good responders after radiochemotherapy for low rectal cancer. Patients selected after radiochemotherapy with clinical good response, completed by LE for pathologic examination of the tumor response may benefit from organ preservation without missing positive lymph nodes.

Predictors of Radiotherapy-Related GI Toxicity from Anal Cancer DP-IMRT: Secondary Analysis of RTOG 0529

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Purpose/Objective(s): Radiation Therapy Oncology Group (RTOG) 0529 assessed the feasibility of dose-painted intensity-modulated radiation therapy (DP-IMRT) to reduce the acute morbidity of chemoradiation with 5-fluorouracil (5FU) and mitomycin-C (MMC) for T2-4N0-3M0 anal cancer. This secondary analysis was performed to identify patient (pt) and treatment factors associated with acute and late gastrointestinal (GI) adverse events (AEs).

Materials/Methods: RTOG 0529 treatment plans were reviewed to extract dose-volume data for tightly contoured small bowel (SB), loosely contoured anterior pelvic contents (APC), and uninvolved portions of colon outside the clinical target volume (UC). T-tests were performed to evaluate differences in the mean absolute volumes of each critical structure receiving doses ≥ 5 to 60 Gy (V5-V60) in 5 Gy increments between pts with and without ≥ grade (G) 2, acute and late GI AEs, and ≥G3 acute GI AEs using the NCI Common Terminology Criteria, version 3. Differences in mean dose to SB and APC were also evaluated for acute and late ≥G2 and ≥G3 GI AEs. Acute is defined as ≤ 90 days from the start of treatment and late is > 90 days. Additional factors (age, location, gender, race, Zubrod, grade, size, stage, prone vs. supine position) were evaluated in multivariate (MV) logistic regression (acute AEs) or Cox proportional hazards models (late AEs) to evaluate correlation with GI AEs.

Results: Among 52 evaluable pts, ≥G2 acute, ≥G2 late, and ≥G3 acute GI AEs were observed in 35, 17, and 10 pts, respectively. Trends (p<0.05) towards statistically significant associations were observed between: ≥G2 acute GI AEs and SB dose (V20-V40); ≥G2 late GI AEs and APC dose (V60); ≥G3 acute GI AEs and APC dose (V5-V25), increasing age, tumor size >4cm, and worse Zubrod. SB and APC dose parameters remained correlated with GI AEs on MV analysis. Treatment in the prone vs. supine position correlated with lower SB V10-V35 and APC V5-V20, although no significant differences in GI AEs were observed.

Conclusions: Acute and late GI AEs from 5FU/MMC chemoradiation using DP-IMRT correlates with RT dose to the SB and APC. Further analysis is underway to determine critical structure cut-point parameters that may aid treatment plan optimization for anal cancer DP-IMRT.

Acknowledgment: Supported by RTOG U10 CA21661, CCOP U10 CA3742 and ATC U24 CA 81647 NCI grants.

Interim Analysis of a Phase II Clinical Trial of Induction Gemcitabine/Capecitabine followed by SABR in Borderline/Locally Advanced Pancreatic Adenocarcinoma

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Purpose/Objective(s): Stereotactic ablative radiation (SABR) with its shorter treatment times & conformality is a promising treatment modality for patients with locoregionally confined pancreatic ductal adenocarcinoma (PDA). We conducted a prospective, single-arm phase II clinical trial to evaluate the safety, feasibility and efficacy of induction chemotherapy (ICT) followed by SABR, in subjects with borderline resectable (BR) and locally-advanced (LA) PDA. 2 year local progression-free survival (LPFS) is the primary end point and follow up is ongoing.

Materials/Methods: Patients (pts) had to have biopsy-proven PDA (LA or BR). ICT consisted of four 21-day cycles of gemcitabine (d1&8 1000 mg/m2) and capecitabine (days 1-14, 650 mg/m2---BID). Pts were restaged within 4 weeks post-ICT by CT imaging and, and continued to SABR if no mets or progressive disease were identified. SABR dose was 36 Gy in 3 fractions to the planning target volume (PTV) including a 2mm expansion around the gross tumor. Patients were re-staged 4 weeks following SABR to determine resectability.

Results: All 34 enrolled pts (18 BR/16 LA) are included in this analysis. The average age was 71, 56% female. All 4 cycles of ICT were completed in 91% (n=31) of pts. 3 pts did not receive chemotherapy (1 died during ICT because of an arterial occlusion, 1 died after consent, 1 had a MI during chemotherapy). There were 3% (n=1) grade 3 GI, 10% (n=3) grade 3 hematological, and 3% (n=1) grade 4 hematological toxicities with ICT. All 31 pts who completed chemotherapy also completed SABR. Mean PTV was 24.3 cm3 with no acute SABR toxicities. Of those 31, 40% (n=12-10BR, 2LA) proceeded to pancreaticoduodenectomy- 10/10 BR and 1/2 LA patients had R0 resections; pCR in 1 BR. 8 patients with BR disease did not receive surgery (3 with progressive local disease, 1 had a myocardial infarction, 1 declined surgery, 2 developed metastatic disease, 1 unresectable at surgery). There were 5.8% (n=2) grade 3 (pseudoaneurysm and hepatic abscess), 5.8% (n=2) grade 4 (ICU admission for CVA and portal vein thrombosis) post-operative toxicities (Clavien scoring). For BR pts 1-year LPFS was 86%, and median freedom from any recurrence was 25.5 months. For LA pts 1-year LPFS was 100%, and median freedom from any recurrence was 22.5 months. Out of 20 evaluable patients with both pre-ICT and post SABR CA 19-9 values, the mean value decreased from 867 to 177 (p=0.009) with decreases >50% in 7/9 BR and 7/11LA cases.

Conclusions: This is the first prospective phase II study to investigate the feasibility and efficacy of induction chemotherapy, SABR, followed by surgical resection. This approach appears promising in facilitating an R0 resection in BR patients with acceptable toxicity. With continued follow-up, the efficacy of this approach can be defined.