Role of adjuvant radiotherapy following neo-adjuvant chemotherapy (NACT) and surgery in oesophageal cancer – a multi-centre retrospective cohort study

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Objectives:
Positive circumferential resection margin (CRM) (R1), defined as CRM <1mm, following surgery for oesophageal cancer, is an associated predictor of poor survival. In the UK where NACT is considered standard of care, R1 rates of 35-40% has been reported in studies of NACT (OE02,OE05). Internationally, pre-operative chemoradiotherapy (CRT) is increasingly being considered standard of care, following the CROSS trial which showed a significant survival advantage compared to surgery alone and a R1 rate of about 10%. The role of selective adjuvant (C)RT in patients with R1 margin following NACT is unclear. We investigated the survival outcomes and effect of adjuvant radiotherapy in patients undergoing oesophagectomy, including those with R1 margin as a subgroup.

Methods:
Retrospective analysis from two high-volume tertiary referral centres. All patients who underwent oesophagectomies at University Hospitals Bristol (July 08 to June 2013) and Oxford University Hospitals (April 2009 to November 2013) were included. NACT consisted of 2 cycles of Cisplatin and 5-FU or 3 cycles of Epirubicin, Cisplatin, Capecitabine for T2+ or node positive disease. Following surgical resection, adjuvant (C)RT was offered to fit patients with R1 resection. Univariate and multivariate Cox proportional hazards analyses were performed, with stratification by centre.

Results:
408 patients were included in the study (Bristol -223, Oxford – 185). Eighty two (20%) had R1 (Bristol – 44 (20%), Oxford – 38 (21%)); the remaining had a complete resection margin (R0). The median OS and RFS among all patients was 67 months (median follow-up: 46 months) and 40 months (median follow-up: 44 months), respectively, and in the R1 subgroup was 19 months (median follow-up: 53 months) and 15 months (median follow-up: 38 months), respectively.

Univariate analyses showed a CRM$\geq$1mm was associated with better survival post-surgery among all patients (OS HR=0.47; 95% CI: 0.34–0.66; p<0.001 and RFS HR=0.46; 95% CI: 0.33–0.63; p<0.001). Furthermore, for R1 patients, adjuvant (C)RT improved OS (median survival (MS) - Surgery (S) vs (Surgery + adjuvant CRT (S+CRT)): 16 vs. 24 months; HR=0.46; 95% CI: 0.24–0.89; p=0.021) and RFS (MS- S vs S+CRT: 12 vs. 17 months; HR=0.5; 95% CI: 0.27–0.92; p=0.026) in the R1 subgroup.

These results were consistent in the multivariate analyses, which also showed that, upon accounting for other prognostic factors, adjuvant CRT improved OS (HR=0.54; 95% CI: 0.30–0.97; p=0.038) and RFS (HR=0.46; 95% CI: 0.26–0.802; p=0.006) in all patients.

Conclusion:
R0 resection rates and survival outcome of patients treated with NACT alone in these two high-volume centres were comparable to outcomes following pre-operative CRT as reported in the CROSS trial (Shapiro et al, 2015) and superior to studies of NACT alone (OEO2, Allum et al, 2009, OEO5, ASCO 2015). Selective use of adjuvant (C)RT in patients with R1 margin improved both OS and RFS. NACT and selective adjuvant CRT for R1 resection is therefore an acceptable alternative to pre-operative CRT for patients with resectable oesophageal cancer, particularly in centres where high R0 resection rates can be achieved.