O-4 Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for colorectal cancer survival, with implications for treating obese patients: The OCTOPUS consortium

C. Slawinski[1], L. Malcomson[1], J. Barriuso[2], H. Guo[1], A. Harkin[3], T. Iveson[4], R. Glynne-Jones[5], C. Van de Velde[6], A. Renehan[2]

[1]University of Manchester, Manchester, United Kingdom; [2]University of Manchester / The Christie NHS Foundation Trust, Manchester, United Kingdom; [3]Cancer Research UK Glasgow Clinical Trials Unit, Glasgow, United Kingdom; [4]University of Southampton, Southampton, United Kingdom; [5]Mount Vernon Cancer Centre, Northwood, United Kingdom; [6]Leiden University Medical Center, Leiden, Netherlands

Background: After curative surgery for colorectal cancer (CRC), some studies indicate poorer survival in obese patients. Adjuvant chemotherapy (ACT) for CRC is commonly capped at a body surface area (BSA) $\geq$2.2m2, potentially reducing chemotherapy average cumulative relative dose (ACRD) and average relative dose intensity (ARDI) in obese patients.

Methods: Individual participant-level data from MOSAIC, SCOT, PROCTORSCRIPT, and CHRONICLE (CRC-ACT) randomised-trials, with derivable BMI, BSA, and chemotherapy doses, were included from the OCTOPUS consortium. ARDI and ACRD were calculated as percentages of actual to expected (full BSA-based) dose intensity (cumulative dose/treatment duration in weeks) or cumulative dose, respectively, averaged across the drugs in the regimen. Two-stage random-effects meta-analyses of linear or Cox proportional hazards regression models were performed to explore BMI-ARDI/-ACRD and ARDI-/ACRD-survival relationships, respectively. The primary outcome was disease-free survival (DFS), and secondary outcomes were overall (OS) and cancer-specific (CSS) survival, in addition to ARDI and ACRD. All models where adjusted for

age, sex, performance status, t-stage and n-stage (in addition to BMI in the survival models).

Results: 7269 patients were eligible. BMI 5kg/m2 increments were associated with a 2.04% reduction in cycle 1 dose (95% CI:-2.45,-1.64; p ACRD 5% increments were associated with improved DFS (HR 0.953 (0.926, 0.980); p=0.001), OS (HR 0.931(0.908, 0.955); $p < 0.001$) and CSS (HR 0.941(0.924, 0.959); $p < 0.001$) survival. However, no significant relationship was demonstrated for ARDI (DFS HR 1.015 (0.967, 1.065); p=0.552; OS HR 1.035 (0.990, 1.081); p 0.134; CSS HR 1.022 (0.982, 1.064); p =0.282), nor for sex-interactions for both ACRD and ARDI.

Conclusions: ACRD is more important than ARDI in determining survival. Elevated BMI is associated with a reduced cycle 1 dose and a modest ACRD reduction. These indirect effects through under-treatment might explain poorer survival in obese patients, rather than direct effects of obesity resulting from, for example, tumour biology.

Legal entity responsible for the study: The authors.

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