DEPRESSION OF MUSCLE PROTEIN SYNTHESIS (MPS) WITH NO EVIDENCE OF ELEVATED MUSCLE PROTEIN BREAKDOWN (MPB) PRECEDES MINOR MUSCLE WASTING IN EARLY COLORECTAL CANCER


Background and Aims: Baracos group developed a useful method with clinical CT images to investigate muscle wasting. We applied this technique to colorectal cancer patients, in a subset of whom we investigated muscle metabolism.

Methods: We analysed CT images (psosas major, L-3; glutaeus maximus, coccyx) for patients with colorectal cancers (n = 65,73 ± 11y) and patients who proved normal on investigation(n = 56,71 ± 11y). In a subset (n = 18,74 ± 10y) of the cancer patients, we also characterized muscle metabolism by stable-tracer and molecular methods.

Results: In the healthy patients, psosas thickness was 30(28,31) mm (median (95%CI)) and 31(26,30) mm in cancer patients. Normal glutueus thickness was 30(31,36) mm; 29(32,38) mm in patients; normal psosas cross sectional area (CSA) was 2873(2708,3299) mm2 and in patients was 3049(2561,4153) mm2. In metabolism subset, psosas thickness was 30(28,35) mm, glutueus thickness was 36(32, 38) mm; psosas CSA was 2973(2442, 3074) mm2. Thus in patients with early colorectal cancer significant wasting could not be detected by comparison with age-matched controls. However, the metabolic subset, despite only minor losses of leg muscle (2–15 g/day), showed “anabolic resistance” of MPS (fed state: 0.030 ± 0.003 vs. 0.071 ± 0.003 %/h) with no evidence of elevated MPB.

Conclusion: Establishment of muscle metabolic dysfunction precedes major sarcoenina in colorectal cancer.

DICHLOROACETATE INDUCES APOPTOSIS AND CELL-CYCLE ARREST IN COLORECTAL CANCER CELLS BUT NOT IN NON-CANCEROUS CELLS

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Introduction: Cancer cells undergo increased glycolysis, the so-called ‘Warburg effect’. The aim of this study was to determine if switching metabolism from glycolysis towards mitochondrial respiration would preferentially induce apoptosis in colorectal cancer cells and examine the underlying mechanisms.

Methods: Representative colorectal cancer and non-cancerous cell lines were treated with Dichloroacetate, a non-specific inhibitor of pyruvate dehydrogenase kinase (PDK), which promotes mitochondrial respiration. Cellular proliferation, apoptosis, cell-cycle profile, mitochondrial membrane potential (Δψm), and glycolytic metabolism were measured.

Results: 20 mM Dichloroacetate did not affect growth of non-cancerous 293 and HR2 cells, but caused significant decrease in proliferation of all the cancer cells; HT29, SW480, and LoVo (p = 0.009), associated with a significant increase in apoptotic cells, and an eight-fold increase in number of cells in G2 phase amongst cancer cells suggesting induction of G2 arrest. The largest effect on apoptosis was seen in metastatic LoVo cells with 50 mM Dichloroacetate resulting in a 21% (95% CI: 9 to 34) increase in the apoptotic fraction. Dichloroacetate reduced lactate levels and decreased Δψm in cancer cells (p = 0.043).

Conclusions: Dichloroacetate induces apoptosis in colorectal cancer cells via the mitochondrial pathway. Further research investigating inhibition of specific isoforms of PDK, known to be differentially upregulated in cancer, is underway.

NEUTROPHIL-LYMPHOCYTE RATIO – AN INDEPENDENT PREDICTOR OF SURVIVAL IN BREAST CANCER

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Aims: Higher neutrophil-lymphocyte ratios (NLR) on pre-operative bloods have been shown to be associated with worse survival after resection of colorectal and other cancers. This study aimed to determine if NLR can be used as an independent predictor of survival in breast cancer.

Methods: Retrospective review of curative resection for breast cancer between Jan 2001–Dec 2003 was performed. Prognostic factors were evaluated by univariate Kaplan–Meier models and multivariate Cox regression model of survival to test for independence.

Results: 406 underwent resection. 361 had bloods done pre-operatively and were included. 357 females and 4 males. Mean age 59.2 (29–95) years. The median follow-up was 89 (72–108) months. 271 patients had NLR < 3 and 90 had NLR >3. Percentage deaths for NLR < 3 (n = 57, 21.0%) and NLR >3 (n = 34, 37.8%). Mean survival was 97.4 (94.7–100.3) months in patients with NLR <3 versus 88.7 (82.1–95.3) months in those with NLR >3. On multiple regression analysis, NLR remained a significant prognostic indicator, after adjusting for NPI (Nottingham Prognostic Index) and other factors (P = 0.0261, 95% CI = 0.7463–0.9216). On Kaplan-Meier survival analysis of the subsets of groups [Log-Rank (Mantel-Cox) Chi-Square–6,211, degree of freedom–1, P = 0.013].

Conclusions: Pre-operative NLR is an independent predictor of survival in breast cancer in this series.

131 I-MIBG, A NOVEL APPROACH IN NEUROBLASTOMA TREATMENT

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Neuroblastoma is the commonest extra-cranial solid-tumour of peripheral sympathetic NS in children and leading cause of cancer-related deaths in childhood(1–4Y). Tumour-cells take up, store and secrete catecholamine metabolites and express the norepinephine transporter, making metaiodobenzylguanidine (MIBG)-an analogue of norepinephine- an ideal tumour-specific agent for imaging and therapy when labelled with 131I or 123I. This randomised controlled trial presents our experience in using 131I-MIBG upfront therapy in diagnosing and treating Neuroblastoma. Thirty-four patients had their treatment up-fronted by 3 cycles of 131I-MIBG every 21 days guided by haematological recovery (Group A) followed by first-line chemotherapy. Surgical intervention varied according to response aiming at complete tumour-clearance. Follow-Up (24–60 Months) and results were compared to the control-group of 36 patients who had their treatment after a diagnostic 131I-MIBG approach. Group-A demonstrated an objective response to initial 131I-MIBG therapy of 44.10%, while group-B missed this response, not only the overall OR. following completion of three main lines of treatment was significantly higher in the