AB065. SOH22ABS054. Oesophageal cancer surgery promotes a pro-tumour, pro-metastatic phenotype that is partly inhibited by immunotherapy

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Background: Adjuvant immunotherapy for oesophageal cancer is set to become a standard of care following the Checkmate-577 trial proving the efficacy of adjuvant nivolumab. Scientifically, the key mechanisms are unclear. This study profiled systemic anti-/pro-tumour immunity and circulating pro-metastatic factors perioperatively in patients, and the impact of immune checkpoint blockade on key pathways using an *ex vivo* model system.

Methods: Systemic immunity in oesophageal cancer patients (n=14) was immunophenotyped prior to surgery [postoperative day (POD)-0] and POD-1, -3, -7 and week-6, using flow cytometry. Longitudinal serological profiling was conducted by multiplex ELISA characterising systemic immunity and pro-metastatic signalling. The cytolytic ability of circulating lymphocytes against oesophageal cancer cell lines was assessed with and without immunotherapies; nivolumab/ipilimumab.

Results: PD-1+ and CTLA-4+ T-cells peaked on POD-1, and significantly decreased by week 6 (P<0.01). Circulating soluble checkpoints PD-1, PD-L2, TIGIT and LAG-3 significantly (P<0.001) increased from POD-3, with decreases in Th1 cytokines (IFN-γ, IL-12, p40, IL-1RA, CD28, CD40L) and increases in Th-2-cytokines (IL-4, IL-10) observed (P<0.001), and a return to baseline by week 6. Circulating pro-inflammatory cytokines (TNF-α, MCP-1) and pro-metastatic factors (VEGF-α, FLT-1, Tie-2, PIGF) significantly (P<0.001) increased in the immediate post-operatively. In an *ex vivo* model, the cytolytic ability of circulating lymphocytes peri-operatively (P<0.01) was propagated with the use of nivolumab/ipilimumab. Surgery decreased the frequency of circulating Th-1 like cells, an effect inhibited by nivolumab/ipilimumab.

Conclusions: Major oesophageal cancer surgery promotes a switch from Th1 to Th2 cellular immunity, dampening the cytolytic ability of T-lymphocytes, promoting the elaboration of pro-metastatic signalling factors systemically. In an *ex vivo* model, PD-1/CTLA-4 inhibition induced a shift to a Th1-like cytotoxic phenotype, highlighting a potential pathway through which such therapies can affect minimal residual disease, and a need to study optimal timing of adjuvant therapy.

Keywords: Immunosuppression; oesophageal cancer; oncology; perioperative; surgery

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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