BAGP research grant proposal outline: BIO-INTERLACE

Title: BIO-INTERLACE: Validation of molecular features that predict outcome in patients undergoing chemoradiotherapy for locally advanced cervical cancer.

Background:

The INTERLACE trial investigated the addition of induction chemotherapy (IC) to curative chemoradiation (CRT) in patients with locally advanced cervical cancer (LACC)[1]. An optional translational consent was taken which allows access to tissue for research purposes. Up to 132 tissue blocks from diagnosis in patients who underwent CRT for LACC are therefore available for use. In addition, we have more 64 months median survival and toxicity follow up data as well as complete radiotherapy plans and parameters.

Despite an increase in survival with IC, 27% of patients still relapse within 5 years of CRT[1]. We therefore aim to explore the biological reasons behind variation in survival, as well as toxicity, radiosensitivity and chemosensitivity. By understanding indicators of poorer prognosis or poorer response to certain treatments we may be able to define cohorts of patients who benefit from additional therapy such as boosted radiation dose, immunotherapy or other targeted therapy.

BIOEMBRACE analysed 264 patients who underwent chemoradiotherapy for LACC within the European EMBRACE trial and presented that, using immunohistochemistry, p16 negativity predicts poorer radiotherapy response and PDL1 and L1CAM expression is associated with reduced pelvic and local control[2]. However, their PDL1 assay is the 1:100, Abcam, clone SP142 which detected less than 20% of patients as PDL1+ compared to the standard 22C3 clone used in clinical practice which defines more than 90% as positive.

In addition, p53 has been investigated as a potential prognostic marker in cervical cancer due to its relationship to p16 and HPV status (p16 positive/HPV related cases often show markedly reduced p53 staining[3]). Overexpression of p53 has been associated with a poorer prognosis and may add to this IHC panel predicting treatment response and outcomes.

Hypothesis

We aim to validate the BIO-EMBRACE findings in our cohort of 132 patients through replications of their analysis in this UK cohort as well as review the role of p53. We therefore hypothesise that in this UK cohort of patients undergoing CRT p16 negative (and possibly p53 overexpressed) patients experience a poorer radiotherapy response and PDL1 and L1CAM expression is associated with reduced pelvic and local control.

Methods

Immunohistochemistry will be performed for p16, PDL1 (SP142 and 22C3 clones), L1CAM and p53 for all of these samples. Interaction between p16, PDL1, L1CAM, p53, HRCTVD90

(radiotherapy dose), HRCTVD90 volume where possible (radiotherapy response), local and pelvic control will be analysed. Univariate and multivariable analysis will be performed.

Expected Result

Our results will hopefully validate the BIO-EMBRACE findings and may show the additional role of p53. This will lead to subsequent work analysing radiotherapy dose patterns and the impact of IC on any of these findings. This could potentially lead to a selection criteria for patients benefitting more from the addition of IC or aiding the selection of patients who are in need of further investigation with alternative therapy such as immunotherapy. In addition, moving forwards, we plan to use next generation sequencing or spatial transcriptomics to generate new hypotheses regarding genomic and molecular pathways that may be associated with outcomes in this patient cohort.

References (max 5)

1: McCormack et al. LBA8 A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: The GCIG INTERLACE trial. Ann Oncol 2023;34(Suppl 2):S1276. Presidential presentation at ESMO 2023.

2: Chopra et al. AS03 Molecular features predicts outcomes in multicentric international study of chemoradiation and MRI based image guided brachytherapy for cervical cancer (EMBRACE): Final analysis from BIOEMBRACE-I. Int J Gynecol Cancer 2023;33(Suppl 4):A24

3: Thompson EF et al. p53 Immunohistochemical patterns in HPV-related neoplasms of the female lower genital tract can be mistaken for *TP53* null or missense mutational patterns. Mod Pathol 2020;33:1649–1659.

4: Zhou et al. The prognostic value of p53 expression for patients with cervical cancer: a meta analysis. Eur J Obstet Gynecol Reprod Biol 2015;195:210-213.