CHIEF SCIENTIST OFFICE

CODE:TCS/20/11

RESEARCH PROJECT BRIEFING

Multiplex methylation analysis of cell-free DNA for early cancer diagnosis

AIMS

Oropharyngeal squamous cell cancer squamous cell carcinoma (OPSCC) is a cancer of the throat that can be associated with human papilloma virus (HPV) infection. It is increasingly prevalent due in part to an increase in frequency of HPV-related disease. Current standard of care rests on conventional clinical and imaging assessments, with survival rates that have changed little in recent years. This award addresses the question: “Can liquid biopsy, the analysis of cell-free DNA, represent a minimally invasive approach to management of OPSCC that can improve diagnosis, monitoring and management options in both HPV-positive and HPV-negative disease?”

KEY FINDINGS

- We have shown that longitudinal following of patients with HPV liquid biopsy blood assays can predict the outcome of primary treatments and can detect disease recurrence or progression prior to clinical presentation or imaging evidence.
- From the work of the study, we have published two peer-reviewed papers, with a further two papers at an advanced stage of preparation. In addition, the results have been presented at five separate national and international meetings, with awards made to the presenters.
- An outstanding biorepository of patient samples has been collected for HPV+ve and HPV-ve disease, with a total of 1187 samples collected to date from a total of 236 patients. These samples have formed the basis of the published work and ongoing collaborative work, with two separate collaborations established with the Institute of Cancer Research (London) and a further collaboration with the Moffat Cancer Centre, USA. This biorepository collection has been possible initially through samples collected in Southeast Scotland under the NHS Lothian Bioresource protocol, subsequently extended to a pan-Scotland research ethics protocol, enabling Scotland-wide recruitment of patients and collection of samples.
- We have had excellent participation of clinical trainees and science undergraduates, with involvement of four academic Foundation Year ENT doctors, one fourth year medical student and three biomedical science undergraduates, one of whom received a distinction and subsequent first-class honours degree following her thesis on the project.
- Finally, the work of the study on HPV+ve disease has been widely used as an Multidisciplinary Team discussion and clinical management tool across Scottish regions, leading to the assays being transferred to the NHS HPV reference lab where assays in the last year of the project were carried out. The process of moving these assays into routine NHS care is being explored by engagement with the Scottish Government through the Genome Testing Group, Health Improvement Scotland, and in collaboration with the Institute for Cancer Research through NHS England.

WHAT DID THE STUDY INVOLVE?

- Recruitment: An outstanding new biorepository of patient samples has been collected for HPV+ve and HPV-ve head and neck cancer, with a total of 1187 samples collected to date from a total of 236 patients.
- Laboratory assays: We carried out testing of five HPV subtypes (known as serotypes) in the DNA in the bloodstream, known as plasma cell-free DNA, on 717 samples from 114 patients with HPV+ve disease and exome sequencing of tumours from 12 patients with HPV-ve disease. This is a new type of analysis, only recently possible for this cancer.
- Results: In HPV+ve disease, we were able to divide our cohort into complete responders, partial responders and those with progressive disease and were able to calculate the predictive value of a single post-treatment positive result/consistently negative results (55% positive predictive value, 99% negative predictive value); and the predictive value of consistently negative/persistent positive results (100% positive predictive value, 99% negative predictive value).
- These results have led to transfer of the assays for HPV+ve disease to the Scottish NHS and applications to Health Boards for long-term funding for routine use in NHS patients.
- In HPV-ve disease, our biorepository and preliminary exome sequence data have led to a new collaboration with the Institute of Cancer Research (London) to investigate the predictive value and clinical applicability of liquid biopsy for patients with HPV-ve head and neck cancer and the genomic evolution of radioresistant disease.
- We have had strong engagement with the patients and the public, for which the main outputs are a video broadcast on STV with one of the patients in our studies as an interviewee alongside the Principal Investigator I and Co-Investigator; a Daily Mail article published in May 2022 with subsequent patient engagement and a legacy for our ENT equipment totalling £10,000; and a patient survey of views on management of head and neck cancer and their experience of our liquid biopsy research.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

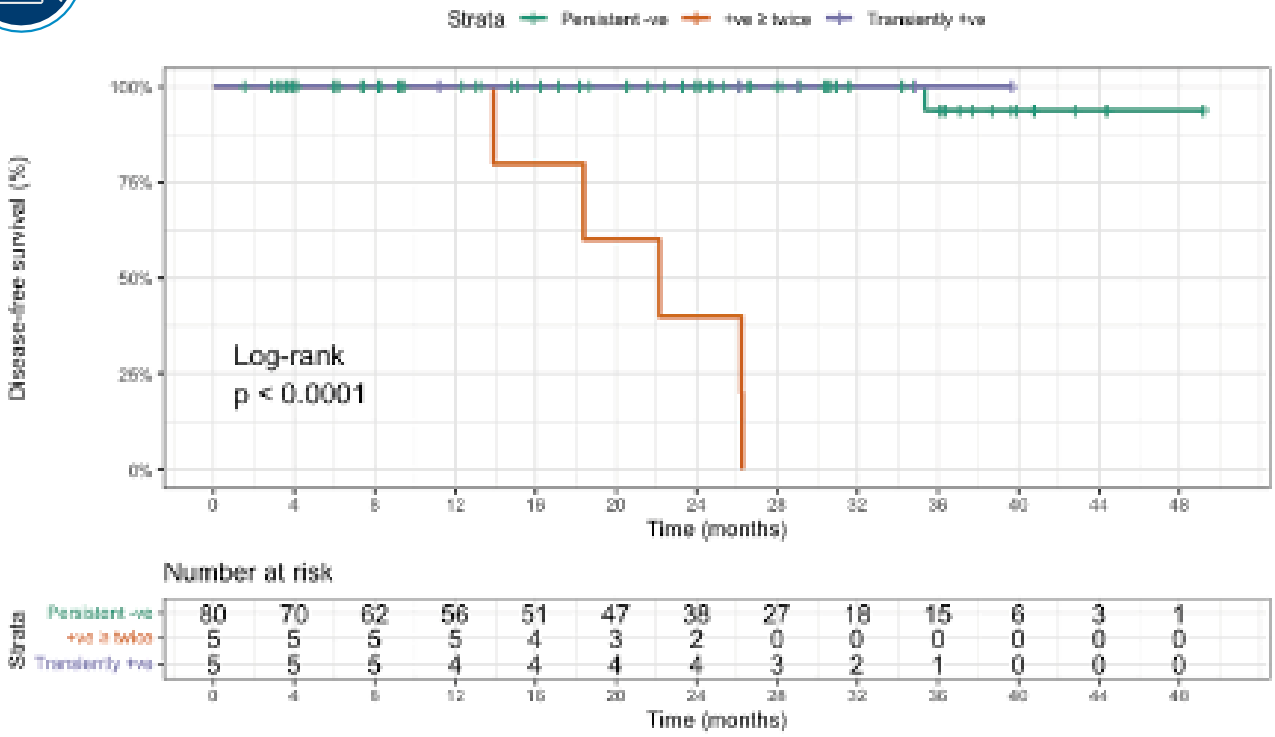

Figure 1. Disease-free survival of complete responders

Figure 1 shows the highly significant predictive value of our HPV liquid biopsy assay as an early marker of disease progression in those whose imaging results had indicated a complete response. Positive and negative results refer to whether or not HPV DNA could be detected in the DNA extracted from the patient's blood sample

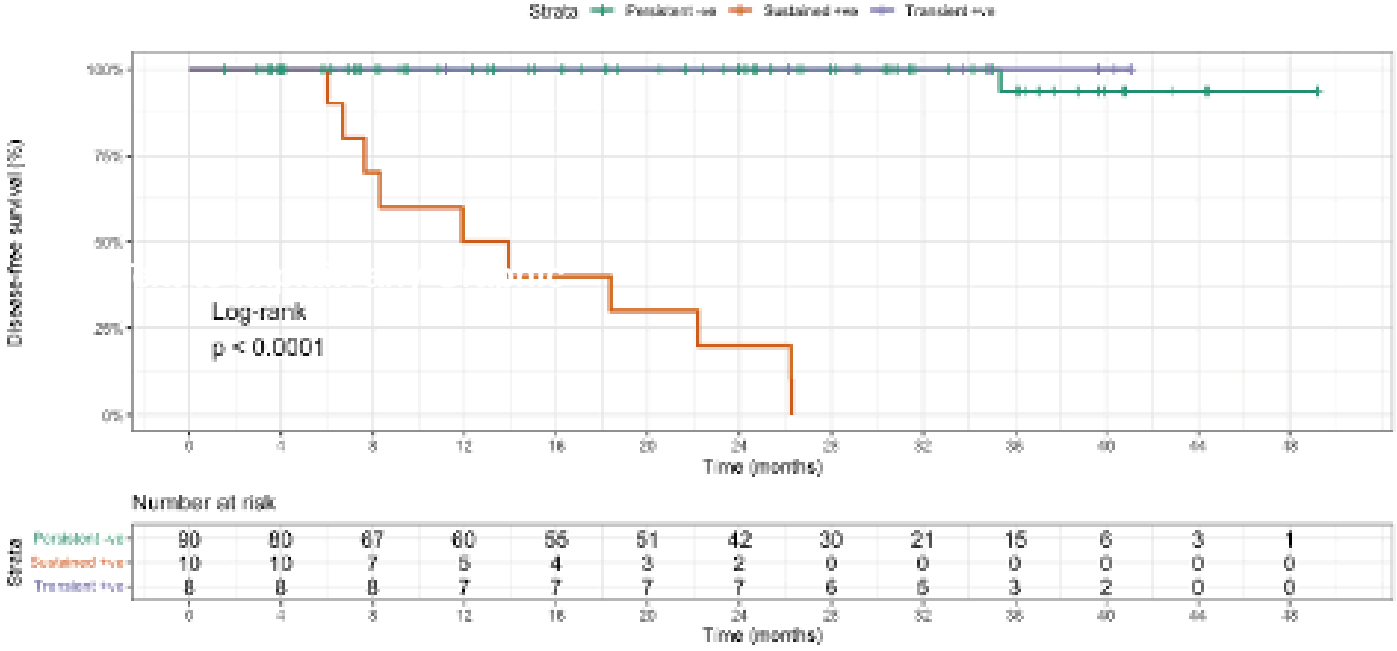

Figure 2. Disease-free survival stratified by liquid biopsy follow-up

Figure 2 shows that patients with sustained negative or only transiently positive liquid biopsy results have >95% disease-free survival at 40 months after primary treatment compared to 0% disease free survival at 28 months in those with sustained positive results.

WHAT IMPACT COULD THE FINDINGS HAVE?

Patients

The impact of the study for patient care is considerable. We have shown that our assay is able to perform as well as invasive tissue-based histology or PCR assays for definition as to whether a particular head and neck tumour is HPV+ve or -ve. This means that, if incorporated into routine care, a diagnosis could be made from a blood test rather than a surgical procedure. Second, we have shown that longitudinal following of patients with HPV liquid biopsy blood assays can predict the outcome of primary treatments and can detect disease recurrence or progression often many months before conventional clinical or imaging detection. These results have been highly reassuring to the patients concerned who have been started on systemic chemotherapy and immunotherapy many months earlier than would have been the case without the liquid biopsy study. In other cases, difficult management decisions, for example when imaging results are uncertain or suggest the possible need for surgical neck exploration, assay results have been highly informative and could avoid the need for surgical intervention. We are currently carrying out a meta-analysis with the suggestion that these results have implications for clinical guidelines.

Policy and practice

Our results are concordant with other results in the same area by other investigators and our colleagues and collaborators, particularly in the private sector, are now using our assay or similar assays to guide clinical management. However, the consensus in the oncology field is that to be large prospective randomised clinical trials are required for this to be incorporated into routine clinical practice.

Our study has received prominence in the field and, using the data produced by this trial and through health economic modelling, proposals are being made to change the standard of care by incorporating these assays, which hold the promise of both improving clinical care and simultaneously offering the opportunity for cost saving.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Our results have already been published in two peer-reviewed papers and two further papers are at an advanced stage of preparation. A large-scale systematic meta-analysis is also in preparation. The results have already been presented at five national or international meetings as abstracts with awards made to the presenters for the best British Association of Head and Neck presentation, the best student presentation at ENT (Ear, nose and throat) Scotland and the Otolaryngology award at the Royal Society of Medicine Annual Head and Neck conference.

In addition, a patient survey has indicated the results are valued by patients who support the incorporation of the work into routine clinical practice. We are currently engaging with funding agencies and patient groups (the International Swallows Society) to establish these future clinical research studies and our participation in them.

CONCLUSION

Overall, the study has had important research and PPI impacts for the diagnosis, management and surveillance of HPV+ve head and neck cancer. The work is likely to be included in future patient guidelines for management of this condition. Our work on HPV-ve negative cancer is ongoing, but substantially facilitated by the exceptional biorepository collected under this funding. The ensuing collaborations, now underway, stand to make a comparable impact on the diagnosis and management of patients with the harder to treat HPV-ve disease.

RESEARCH TEAM & CONTACT

Professor Tim Aitman
Mr Iain Nixon

Institute of Genetics and Cancer, University of Edinburgh, Crewe Road South, Edinburgh. EH4 2XU.

tim.aitman@ed.ac.uk

Additional Information

Project End Date: 31st May 2024

Total award: £299,412