Harnessing head and neck cancer genomics for personalised medicine

BY LUC MORRIS

Luc Morris updates us on the future of cancer diagnosis and treatment, which lies in "personalised oncology", where specific molecular alterations of each tumour will be identified, and matched with actionable alterations in existing therapies, ushering in the era of precision oncology.

In the past five years, our understanding of the genetic alterations linked to the development of head and neck squamous cell carcinoma (HNSCC) has expanded dramatically. This is attributable to a number of seminal studies, carried out by individual research groups, as well as international collaborative efforts by The Cancer Genome Atlas and The International Cancer Genome Consortium. These findings have opened up interest in what has been termed "personalised oncology." This term implies a practice of oncology in which clinicians profile patients' tumours to uncover specific molecular alterations, and then match any identified, actionable alterations to existing therapies or clinical trials. However, achieving this objective requires a critical biologic knowledge base that remains elusive, and optimising the logistics of profiling patient tumours in a clinically acceptable timeframe. This article will describe our field's progress toward the goal of personalised oncology for HNSCC.

Entering an era of personalised oncology

Achieving the practice of personalised medicine in oncology requires a number of critical steps:

1) Defining the landscape of molecular alterations in HNSCC
2) Profiling molecular alterations within individual patient tumours at the time of diagnosis, within a clinically acceptable processing time
3) Understanding the biologic function and clinical ramifications of these alterations
4) Linking alterations in patient tumours to existing or experimental therapeutic strategies
5) Profiling molecular alterations within individual patient tumours on-treatment and after treatment, to elucidate intrinsic or acquired mechanisms of resistance to treatment.

To date, only number one can fairly be said to have been accomplished to some degree. Many cancer centres are beginning to roll out clinical platforms to address number two. These two endeavours are necessary first steps to developing a catalogue of molecular alterations in patients with HNSCC, which can then be studied in more biologic and clinical detail, in order to match our genomic findings with biological processes that can be targeted with new treatments.

The landscape of molecular alterations in HNSCC

The first two large-scale sequencing efforts in HNSCC identified a number of recurrently mutated genes [1, 2]. The majority of these were in tumour suppressor genes rather than oncogenes. HNSCC has been identified as possessing the ninth highest average mutational load out of 30 different tumour types studied. Analysing the types of mutations observed can allow us to infer some carcinogenic processes potentially contributing to the development of cancer. In HNSCC, these include mutagenic processes such as tobacco exposure, ageing, UV light, and alterations in the apoplipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) group of enzymes. Each of these processes leave distinctive 'scars' in the genome that can be appreciated when tumours are subjected to exome sequencing [3].

The most definitive study of alterations at the genetic (DNA), expression (RNA), microRNA, and epigenetic (methylation and chromatin state) levels was published by The Cancer Genome Atlas in 2015 [4]. This study of 279 tumours revealed significant differences between HPV-positive and HPV-negative HNSCC. Most notably, there were differences in the common genes altered within each subtype of HNSCC. In general, there tend to be more alterations in HPV-negative tumours. The most commonly altered genes in HPV-negative tumours were very rarely altered in HPV-positive tumours, such as p53 (84% vs 3%), CDKN2A (58% vs 0%), and Cyclin D1 (31% vs 3%). In contrast, the PIK3CA oncogene, commonly mutated in other cancer types, was more frequently mutated in HPV-positive tumours (56% vs 34%). Alterations in selected pathways are summarised in Figure 1.

This analysis was also able to confirm earlier data suggesting that there are distinct subtypes of HNSCC that can be defined by gene expression patterns. These expression-defined subtypes of HNSCC have been named 'Atypical', 'Classical', 'Mesenchymal' and 'Basal'. The Atypical subtype of HNSCC includes nearly all HPV-positive cases, as well as some HPV-negative cases with similar expression profiles. The Classical subtype of HNSCC includes the majority of larynx tumours, as well as some oral cavity tumours, and is strongly associated with patients with heavy smoking histories. This subtype of HNSCC was very similar to the expression profile of lung squamous cell carcinoma. The Basal subtype of HNSCC was marked by inactivation of NOTCH1. And the Mesenchymal subtype of HNSCC showed high levels of alterations in innate immunity genes.

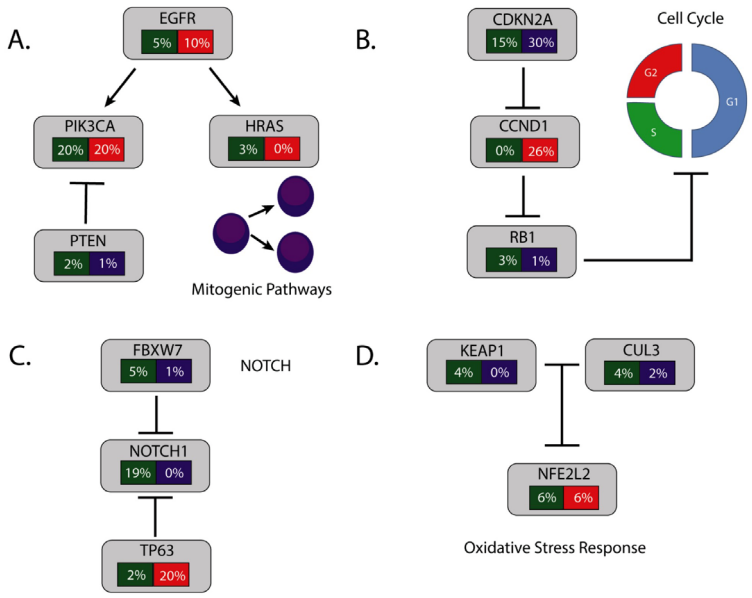


Figure 1: Common alterations in selected pathways in HNSCC.

Green: Frequency of mutations. Red: Frequency of amplification. Blue: Frequency of deletion. (A) Mitogenic pathway alterations. (B) Cell cycle alterations. (C) NOTCH signaling. (D) Oxidative stress response.

Linking alterations to knowledge of biology and new therapies

These early data are instrumental in beginning to understand the commonplace molecular drivers of HNSCC. With correlative investigation, our understanding of biology improves, allowing us to categorise HNSCC tumours according to potentially targetable alterations, which may nominate patients for clinical trials using drugs that target receptor tyrosine kinases (such as EGFR or FGFR), specific oncogenes such as CCND1 or HRAS, or genes in the PI3-kinase pathway (such as PIK3CA and PTEN). As the molecular determinants of tumour response to immunotherapy are worked out, these findings may have additional importance for these therapeutic strategies.

Integrating genomic technologies into clinical practice

At Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA), efforts are underway to introduce routine genomic profiling via next-generation sequencing technology into clinical practice.

The MSK-IMPACT (Memorial Sloan Kettering – Integrated Mutation Profiling of Actionable Cancer Targets) assay is a clinical laboratory test, approved through CLIA (Clinical Laboratory Improvement Amendments) by the Centers for Medicare and Medicaid Services, meaning that the test is suitable for clinical use, provides information that can be reported as part of the clinical record, and used to direct care. Turnaround time for the assay averages two weeks. Since 2014, over 10,000 solid tumours have been successfully profiled as part of routine clinical care at MSKCC using MSK-IMPACT (Figure 2).

The MSK-IMPACT assay is optimised for DNA extracted from archival tissue stored in hospital pathology laboratories – formalin-fixed, paraffin embedded (FFPE) samples. It is a targeted panel including mutation and copy number aberration data with relevance to genes that are functionally relevant to cancer and / or clinically actionable targets. The assay uses hybrid capture technology to perform targeted deep (>200x) sequencing of all 5781 exons and selected introns of 410 key cancer genes, including canonical and selected noncanonical transcripts, as well as the TERT promoter region and 33 introns of 14 recurrently arranged genes [5].

As part of clinical care, over 250 head and neck tumours, mainly recurrent or metastatic cases, have been profiled on the MSK-IMPACT platform. The molecular alterations identified are then reviewed by a multidisciplinary team.

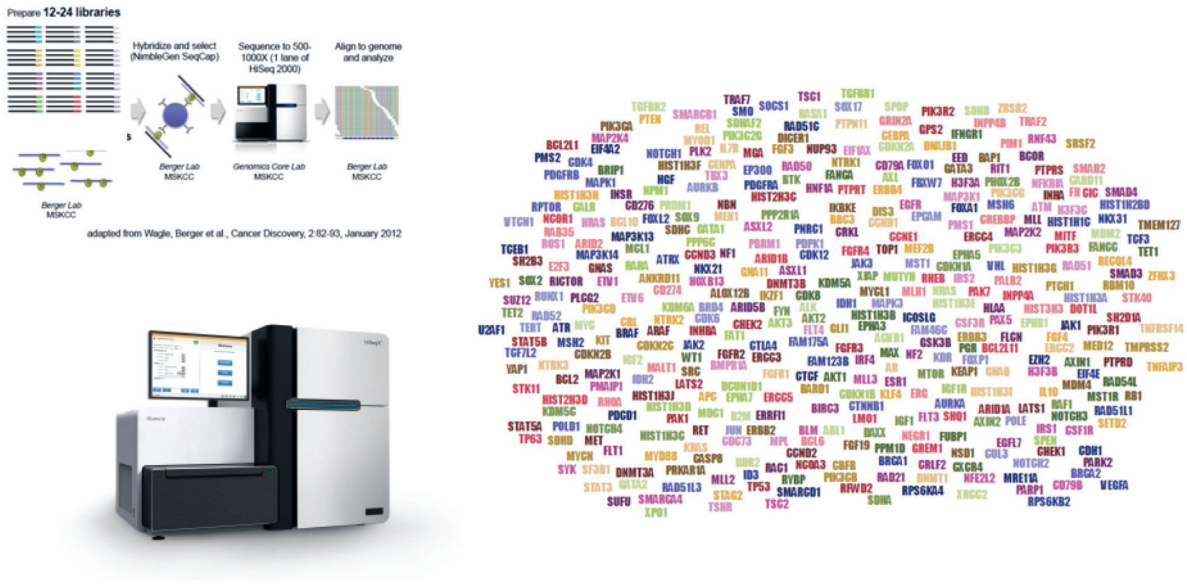


Figure 2: The clinical assay used for next-generation sequencing of cancer genes, copy number alterations and structural variants, at Memorial Sloan Kettering Cancer Center.

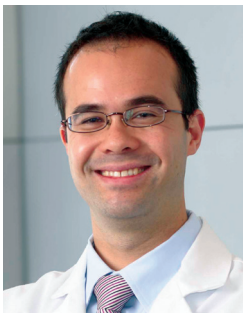
Figure 3: A precision paradigm for clinical trials: molecular alteration-defined "basket studies".

In a substantial fraction of patients, actionable or targetable alterations are identified. These do not always correspond to currently available drugs, but at the present time, more commonly nominate patients for enrollment on "basket studies." Basket studies are therapeutic trials of investigational new drugs, for which patients qualify based on molecular alterations identified within the tumour, rather than traditional factors such as tumour site or histology. Examples of basket trials HNSCC patients currently qualify for include drugs targeting PIK3CA, pan-HER kinases, HRAS, as well as the emerging class of immunotherapeutic drugs that blockade immune checkpoints (Figure 3).

However, in many patients whose tumours are profiled on this platform, we do not identify specific targetable alterations. This reality underscores the most important limitation to the achievement of personalised oncology – we still need to link identified molecular findings to biologic processes. In this respect, continued translational investigation is critical to continued progress against cancer.

SUMMARY

- We are just beginning to develop an understanding of the molecular alterations in head and neck squamous cell cancer
- This is an early but necessary stage in developing the knowledge base to guide research
- As we continue to understand the biologic and clinical significance of these molecular alterations, we will be able to link findings in a patient's tumour to potential therapies or new clinical trials.
- Clinical trials in precision oncology will rely heavily on "basket studies" defined by molecular alterations, rather than cancer type
- Cancer centres are beginning to roll out targeted sequencing clinical platforms that profile individual patient tumours and return results to clinicians in a two week timeframe.



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Declaration of Competing Interests None declared

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