Chapter 24
Innovation and Advances in Precision Medicine in Head and Neck Cancer

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Introduction

The past decade has marked the emergence of precision cancer medicine, a diagnostic and therapeutic approach that aims to comprehensively characterize the clinical, molecular and immunologic aspects of a patient's tumor in order to tailor management [1]. Upon reflection, this approach has encountered a mix of successes with demonstration of clinical utility and failures that have led to disappointments. For the proponents of precision medicine, the glass has been half full and the complete potential of this framework has just begun to be realized. For instance, the genotype-drug matching strategy has potently inhibited oncogenic addiction in some malignancies, yielding spectacular objective responses and sustained clinical benefit. Some examples are disease-specific such as the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) harboring *EGFR* mutations, whereas other indications are histology-agnostic such as neurotrophic tyrosine receptor kinase (NTRK) inhibitors for tumors with *NTRK* gene rearrangements. Furthermore, large scale next generation sequencing (NGS) initiatives to profile cancers have substantively increased knowledge in cancer biology, and provided insights into clonal evolution and mechanisms of therapeutic resistance in oncology. The sharing of clinical and genomic results among institutions worldwide, in efforts such as the American Society of Clinical Oncology (ASCO)'s CANCERLINQ and the American Association for Cancer Research (AACR)'s Project Genomics Evidence Neoplasia Information Exchange (GENIE), has enabled big data learning [2, 3]. Conversely, for the opponents of precision medicine, the proportion of patients who have undergone NGS and ultimately

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benefitted from genotype-target matching has been consistently small, raising concerns on the low cost to benefit ratio of this strategy [4].

The Current Landscape of Large Scale Genomics Based Data Research in HNSCC

Squamous cell carcinoma of the head and neck (HNSCC) represents the sixth most common cancer worldwide. Risk factors include smoking, alcohol and infection with high risk types of human papillomavirus (HPV) [5]. The main treatment modalities include surgery, radiation and chemotherapy, although survival benefit is modest in the advanced setting. Until recently therapeutic options for recurrent or metastatic, platinum resistant HNSCC have been limited, however the emergence of immuno-oncology in this setting has been a welcome addition to the treatment armamentarium for these patients [6, 7]. This has been accompanied by an epidemiological shift, with reduced smoking rates resulting in decreased rates of HPV negative (−) cancers in some countries, whereas others are reporting increasing rates of the biologically distinct, more prognostically favorable HPV-associated (+) HNSCC [8–10]. Despite these seemingly advantageous epidemiological and management shifts, survival rates of high risk locoregionally advanced disease, as well as recurrent or metastatic disease, remain poor. As such it is imperative to further elucidate the molecular pathogenesis of these malignancies, which may facilitate attempts in developing a more tailored, patient specific treatment approach to improve outcomes in patients with advanced HNSCC.

It has become increasingly recognised that HNSCCs are comprised of distinct molecular subtypes [11]. While the development of targeted therapies has been met with success in various malignancies, the diversity of genetic aberrations, the heterogeneous mutational spectrum, and the lack of actionability of the majority of genomic-based alterations observed in HNSCC make a precision-medicine based approach particularly challenging. In an effort to identify further actionable targets, concentrated efforts have been made to provide comprehensive multi-platform, genome wide profiling studies to annotate molecular aberrations in a wide variety of malignancies including HNSCC.

Initial attempts at exploring and curating the etiology and landscape of mutations in human cancer resulted in the development of the Catalogue Of Somatic Mutations In Cancer (COSMIC) (https://cancer.sanger.ac.uk) in 2004. COSMIC includes all the genetic mechanisms by which somatic mutations promote cancer, including coding and non-coding mutations, gene fusions, copy-number variants and drug-resistance mutations [12]. More recently scientific innovation has enabled big data analytics; whole exome capture and massive parallel sequencing of cancer genomes have further augmented our understanding of the mutational landscape of HNSCC. The first reports of whole exome sequencing of HNSCC were published in 2011, which provided a glimpse into the extensive network of molecular changes

underlying HNSCC [13, 14]. These studies demonstrated a mutation rate consistent with that seen in other smoking-related malignancies, and identified the six most frequently mutated genes that may potentially encode key signaling molecules for HNSCC tumorigenesis: *TP53*, *NOTCH1*, *CDKN2A*, *PIK3CA*, *HRAS*, and *PTEN* genes. The true significance of these early studies however was in the validation of large-scale sequencing in exposing fundamental tumorigenic mechanisms.

In 2015 The Cancer Genome Atlas (TCGA) then became the catalyst for systematic characterization of diverse genomic alterations underlying human malignancies, which now represents the most comprehensive integrative genomic analysis of HNSCC. TCGA has yielded numerous novel biological insights, and has had a profound impact on how cancer genomics is now conducted. It utilises a collaborative approach to harmonize data and standardize analyses with the ultimate aim of enhancing our knowledge of cancer biology and pathogenesis. TCGA has profiled 500 HNSCC tumors, and has aided in further characterizing the groups of genes implicated in its pathogenesis, such as genes important for cell survival and proliferation (*TP53, HRAS, EGFR*, and *PIK3CA*), cell-cycle control (*CDKN2A* and *CCND1*), cellular differentiation (*NOTCH1*), adhesion and invasion signaling (*FAT1*) [13–15].

Analyses from the first 279 patients reported copy number alterations (CNAs) including losses of 3p and 8p, and gains of 3q, 5p and 8q chromosomal regions resembling squamous cell carcinomas of the lung [16]. The amplification of 3q26/28 region containing squamous lineage transcription factors, *TP63* and *SOX2*; and *PIK3CA* oncogene is seen in both HPV subtypes, but more frequently in the HPV(+) subtype [17, 18]. HPV(+) tumors were distinguished by novel recurrent deletions and truncating mutations of TNF receptor-associated factor 3 (*TRAF3*), the loss of which promotes aberrant NF-κB signaling [19]. In addition, focal amplification of *E2F1* and an intact 9p21.3 region containing the *CDKN2A* gene were seen. This latter region is commonly deleted in HPV(−) tumors, which also feature co-amplifications of regions containing genes implicated in cell death/NF-κB and Hippo pathways such as 11q13, containing *CCND1*, *FADD* and *CTTN*, and 11q22 containing *BIRC2* and *YAP1*. Recurrent focal amplifications in receptor tyrosine kinases (*EGFR*, *ERBB2* and *FGFR1*) also predominate in HPV(−) tumors. However, a potential limitation in the TCGA data is that most of the sequenced tumors were acquired from early-stage surgical samples, while samples of recurrent/metastatic disease were underrepresented. The latter would likely reveal distinct genetic profiles due to various phenomena including clonal evolution and treatment selection pressures, thus TCGA data may not entirely inform the biological drivers of recurrent and metastatic HNSCC in which most novel targeted agents are currently being tested. Moreover most studies also included only a small number of HPV(+) cases, and many were conducted in heterogeneous patient populations without detailed clinical annotation; as such they may lack the power to determine prognostic and predictive value of genetic alterations identified [18].

An emerging knowledgebase in the current genomic era is the coordinated acquisition and examination of data derived from real world NGS initiatives. The AACR's Project GENIE is another collaborative, international effort aimed at integrating

large scale cancer genomic data and clinical outcomes obtained from participating institutions in the real world setting [3]. To date, the AACR GENIE dataset includes nearly 80,000 de-identified genomic records collected from patients treated at each of the consortium's participating institutions, which are then made available to the global scientific community. The combined dataset now includes data for 80 major cancer types including samples from approximately 1300 patients with HNSCC, and almost 40% represent those collected in the metastatic disease setting. The relative frequencies of the most common somatic mutations in each of the aforementioned databases are quite similar. Some of the frequently mutated genes have matching targeted therapies that may be used to treat HNSCC cases with specific aberrations, generally under the auspice of clinical trials (Fig. 24.1) [3, 20–22].

Biomarker-Based Treatment Strategies

The above mentioned data-sharing platforms have profoundly promoted translational and clinical discovery, providing the impetus for the development of novel therapeutic targets, design of new biomarker-driven clinical trials, and offering a deeper understanding of patient response to therapy. As an increasing number of genetic alterations are identified, one pivotal challenge has been the difficulty matching effective drugs to genomic profiles. Potential targets include driver oncogenes such as *PIK3CA*, of which genomic alterations are associated with both HPV(+) (56%) and HPV(−) (34%) HNSCC cases [23, 24]. Several trials exploring agents that target the PI3K pathway in patients with HNSCC have been largely disappointing, however notable exceptions include combination studies of apelisib (BYL719), a PI3K class I α isoform inhibitor, co-administered with cetuximab; and

Fig. 24.1 The list of common mutations identified in head and neck squamous cell carcinoma in The Cancer Genome Atlas and the frequency of each mutation to date in samples catalogued in the AACR GENIE (American Association for Cancer Research-Genomics Evidence Neoplasia Information Exchange) database. Courtesy of AACR GENIE [3] via cBioPortal [21, 22]

buparlisib, a pan-PI3K inhibitor, co-administered with paclitaxel, where some signals of activity have been observed in early studies [23, 25–27].

The value of DNA-based biomarkers has already demonstrated clinical utility in cancer therapeutics, with many key examples such as anti-HER2 therapies for *HER2* amplified breast cancer and EGFR inhibitors for *EGFR* mutated NSCLC [28, 29]. To date there have been few biomarker-driven trials dedicated to HNSCC. Beyond *PIK3CA*, actionable mutations in other oncogenic driver genes in HNSCC such as *ERBB*, *FGFR*, and *MET* are relatively rare, making it challenging to conduct biomarker directed clinical trials. The EORTC 1559 study (NCT03088059) sought to address this, and is the first international umbrella biomarker-driven study implemented for patients with recurrent and/or metastatic HNSCC [30]. EORTC 1559 (UPSTREAM) attempts to better ascertain upfront the patients who will benefit from a specific treatment, by investigating the activity of immunotherapy or targeted agents in tumors harboring a pre-defined biomarker(s). NGS is carried out to identify somatic mutations and copy number alterations with a custom panel that included 13 oncogenes and tumor suppressor genes (*EGFR, HER2, TP53, PIK3CA, CCND1, NRAS, KRAS, HRAS, PTEN, FGFR1, FGFR2, FGFR3*, and *cMET)*. The analysis also includes p16 and PTEN expression by immunohistochemistry [31]. Based on the molecular aberrations identified and a pre-defined algorithm, patients were allocated to different treatment cohorts including afatinib, palbociclib, niraparib and entrectinib. Patients not eligible for these biomarker-driven cohorts were included in one of the immunotherapy cohorts (monalizumab monotherapy or monalizumab plus durvalumab) [30]. The UPSTREAM study design is dynamic and allows new treatment arms that target other important genetic aberrations, such as *PIK3CA* and *HRAS,* to be added through protocol amendments. Of note recent phase II data evaluating the efficacy of the farnesyl transferase inhibitor tipifarnib in patients with recurrent and metastatic *HRAS*-mutant HNSCC reported objective responses, and thus further investigation in this malignancy is warranted (NCT02383927) [32].

Innovative Clinical Trial Designs

Despite the development and implementation of innovative, precision medicine clinical trial design strategies such as the EORTC 1559 trial described above, to date these trials have largely been centred on molecular matching strategies with predetermined monotherapies [33–40]. Limitations of this approach include low matching rates, possibly due to limited gene panels, restrictive matching algorithms, non-targeting of co-existing resistance aberrations and lack of drug availability [41]. As such combination strategies have begun to be explored in this setting. Traditionally combination strategies have often been employed to induce a synergistic effect and enhance the anti-tumor activity of therapeutic agents, and impede the development of resistance. This approach has been met with some success already, using the aforementioned PI3K inhibitors in combination with both paclitaxel and cetuximab.

Another example is the combination of palbociclib, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor that is associated with objective responses in HPV (−) HNSCC patients when combined with cetuximab [42]. To further explore the customization and personalization of multidrug combination regimens, the I-PREDICT study (NCT02534675) was designed for patients with refractory malignancies [43]. This multi-institutional prospective study utilised tumor DNA sequencing and relied on timely recommendations from a molecular tumor board to provide personalized treatment decisions with combination therapies. The feasibility of this approach was demonstrated with 49% of consented patients receiving individualized combination treatment. Strategies to design clinical trials that test personalized combination regimens in HNSCC are needed.

While the evolution of NGS has augmented the identification of potentially actionable molecular variants, it has become increasingly recognised that these patients may be treated with drugs outside of their approved label indications, and outcomes after employing these targeted therapies may not be systematically collated and shared. The Drug Rediscovery Protocol (DRUP) was implemented to address this shortcoming, with the goal of identifying signals of response in patients with defined tumor types and molecular variants, who are being treated with anticancer drugs outside of their approved label [44]. The study reported an overall rate of clinical benefit (defined as complete or partial response, or as stable disease beyond 16 weeks) of 34% in 215 treated patients, comprising 136 patients who received targeted therapies and 79 patients who received immunotherapy. The overall median duration of clinical benefit was 9 months (95% confidence interval of 8–11 months), including 26 patients who were experiencing ongoing clinical benefit at data cut-off [44]. This trial again demonstrated feasibility of multidrug precision oncology trials, and facilitated the defined use of approved drugs beyond their labels in rare subgroups of cancer.

Similarly, the Targeted Agent and Profiling Utilization Registry (TAPUR) (NCT02693535) study, led by ASCO, was also designed to describe efficacy and toxicity of commercially available, targeted anti-cancer drugs prescribed for treatment of patients whose tumors have a genomic variant known to be a drug target, or to predict sensitivity to a drug [45, 46]. Patients were matched into multiple parallel cohorts defined by tumor type, genomic alteration, and drug. Examples of drug targets and respective treatment arm include *MET* (Crizotinib), *CDKN2A* (2 arms – palbociclib and abemaciclib) and *ERBB2* (trastuzumab and pertuzumab). The Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR) (NCT03297606) is a Canadian Cancer Trials Group led study that leverages existing clinical genomic profiling platforms, and also aims to test the activity of commercially available targeted agents in patients with advanced cancers with 'druggable' mutations [47]. Cohorts are again defined by tumor type, genomic alteration and matched drug treatment. Examples of those with potential relevance to HNSCC include *MET* (crizotinib), *EGFR* (erlotinib), *CDKN2A/CDK4* (palbociclib), *FGFR* (sunitinib), *PIK3CA* (temsirolimus) and *ERBB2* (trastuzumab and pertuzumab).

An innovative development in the pursuit to identify druggable targets involves functional testing, such as small interfering RNA (SiRNA) and drug libraries on

patient derived cell cultures [48]. siRNAs may be used as tools to study single gene function both in vivo and in vitro and represent an attractive new class of therapeutics, particularly against undruggable targets. Xu et al. recently performed comprehensive genomic analyses together with genome-scale siRNA using low-passage tumor cells derived from a patient with treatment-resistant HPV (−) HNSCC. While genomic analysis revealed a heterogeneous mutational profile typical for HPV (−) HNSCC, no drug targets were identified. In contrast, siRNA profiling identified 391 candidate target genes, 35 of which were preferentially lethal to cancer cells. Further studies are warranted but functional profiling may potentially become a useful adjunct to DNA sequencing to guide the therapeutic decision making process for precision oncology.

Adapting to the Evolution of Cancer

For precision medicine to be truly efficacious, it is necessary to recognize and adapt to the evolution of cancer. As discussed this has become an attainable goal due to advances in our ability to comprehensively examine tumor derived material, coupled with the development of increasingly sensitive assays and massive parallel sequencing technologies to detect and analyse cancer specific analytes and their alterations. This has paved the way for the introduction of liquid biopsies, a minimally invasive method designed to assess circulating tumor (ct) DNA, which has received considerable attention as a potential biomarker and surrogate for tissue biopsy [49, 50]. The evaluation of ctDNA is a powerful tool that can be used to longitudinally inform on the real time presence or absence of cancer, compared to a tissue biopsy which only gives a single, static snapshot in space and time. There exists several potential applications for ctDNA, for example monitoring for molecular residual disease (MRD), which describes the detection of cancer-derived molecular biomarkers when the cancer may be radiologically occult (Fig. 24.2). Other examples include early

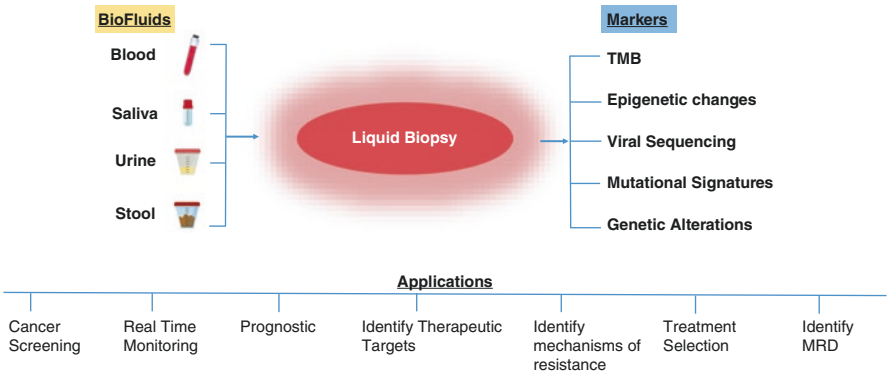

Fig. 24.2 Liquid biopsy sources, markers and applications

assessment of treatment response and further informing on the mechanisms of response or resistance to personalize treatment strategies [50, 51].

It is important to recognize however, that many factors have the potential to influence the abundance and detectability of ctDNA in cancer patients. At diagnosis, anywhere from >90% to <0.1% of plasma DNA is tumor-derived [52]. Tumor type and location influence ctDNA levels, as do prior treatments; other potential confounders such as demographic, comorbidity and environmental factors are less well characterized [51]. Furthermore, ctDNA has a short half-life (of around 1 h) and its kinetics can be complex, thus the timing of blood collection is also significant in order to ensure accurate interpretation of results.

Monitoring in Minimal Residual Disease (MRD)

One of the most appealing clinical applications of ctDNA is to detect cancer recurrence in the MRD setting after definitive local or locoregional therapy, as it offers the opportunity to initiate salvage therapy early (if available), eradicate micrometastatic disease and maximize cure. Observational studies correlating the presence of ctDNA or specific genomic aberrations with disease outcome have shown a prognostic role across multiple tumor types, with positive ctDNA status typically preceding the occurrence of clinical relapse by a few months [53]. In addition to somatic alterations, other cancer-specific biomarkers that may potentially be evaluated by ctDNA include mutational signatures, tumor mutational burden, tumor associated epigenetic changes and methylation patterns, and viral sequencing (Fig. 24.2) [50]. This has been coupled with the development and maturation of technologies and their associated platforms designed to facilitate this evaluation, such as NGS, Digital-PCR, Real-time PCR and mass spectrometry. Wang et al. previously demonstrated feasibility of this approach in HNSCC patients, detecting tumor DNA in postsurgical patients months before the onset of clinical recurrence [54]. More recently ct HPV DNA was longitudinally monitored in patients with HPV associated oropharyngeal cancer post treatment with curative intent to explore its role as a potential biomarker in detecting recurrence, and demonstrated high positive and negative predictive values as a post treatment surveillance strategy [55].

Selecting Patients for Personalized Treatment

In addition to the above applications, ctDNA offers insight into genomic changes in the tumor that may guide therapeutic decisions. ctDNA data generated using high-throughput NGS panels can provide value by directly identifying known or new actionable mutations for genotype–drug matching. For example, ctDNA has been incorporated into standard of care as a less invasive alternative to tissue biopsy for detecting the *T790 M* mutation in *EGFR* mutant NSCLC patients who are

progressing on first-generation tyrosine kinase inhibitors [56]. The B-FAST trial is a phase 2/3 multicentre multi-cohort study evaluating the safety and efficacy of targeted therapies or immunotherapy as single agents, or in combination, in participants with unresectable, advanced or metastatic NSCLC (NCT03178552). Patients were enrolled into four specific molecularly defined treatment cohorts based on identification of genetic alterations using only blood-based NGS [57]. Studies similar to the B-FAST design can be extrapolated to HNSCC to enable precision medicine evaluation using ctDNA as a minimally invasive tool.

Prediction of Treatment Outcome

Early changes in ctDNA dynamics after treatment can inform on therapeutic efficacy, as demonstrated in a retrospective analysis of samples from the phase III PALOMA-3 trial in advanced estrogen-receptor-positive breast cancer. A decline in PIK3CA ctDNA levels compared to baseline after 15 days of treatment with palbociclib and fulvestrant was predictive of progression-free survival [58].

The incorporation of ctDNA into clinical trials of immune checkpoint blockade enables the evaluation of its role as a predictive biomarker. The INSPIRE trial (NCT02644369) is a pan-cancer study which collected tumor and ctDNA samples to correlate with clinical outcome in patients treated with pembrolizumab [59]. A bespoke ctDNA assay was used, whereby 16 patient-specific somatic variants were identified based on paired pre-treatment normal-tumor whole exome sequencing. Change in ctDNA, collected at about 6–7 weeks post initiation of pembrolizumab, compared to baseline, was strongly associated with clinical efficacy parameters including objective response, progression-free survival and overall survival in this study [60]. The dynamics of ctDNA may be leveraged to select out patients, including those with HNSCC, who are most likely to benefit from immune checkpoint blockade.

Moving Beyond Genomics in HNSCC

Over the last several years, the increasing recognition of the complexity and molecular diversity of HNSCC has been coupled with the development and expansion of additional high throughput ‘omics’ technologies, such as epigenomics, transcriptomics, proteomics, metabolomics and shotgun metagenomics. These single level omics approaches may individually shed further light on epigenetic alterations, or molecular subtyping of HNSCC tumors based on protein expression, however they are limited in their ability to fully portray the relationship between molecular signatures and the phenotypic manifestation of the hallmarks of cancer [61–64]. Ultimately, by integrating these biomedical frameworks and developing *multi-omics* approaches there exists an opportunity to further expose the intricate molecular

mechanisms underlying HNSCC phenotypic manifestations, and may potentially offer predictive and prognostic value.

Transcriptomics

Transcriptomics is perhaps the most advanced novel omics approach beyond genomics, with techniques such as RNA sequencing (RNA-seq) developed to detect and quantify all RNA transcripts including messenger RNA (mRNA), long noncoding transcripts (LncRNAs) and microRNAs. This has enabled careful scrutinization of their expression profiles and assessment of the impact of their alterations, which may aid in disease classification and progression. In contrast to the static genome, the transcriptome exhibits dynamic changes depending on cellular, environmental, extracellular, and developmental stimuli [64]. The increasing interest to perform transcriptomic profiling to further delineate therapeutic targets is exemplified by the WINTHER trial (NCT01856296) [65]. This was a collaborative international precision medicine study involving investigators from five countries that prospectively matched patients to therapy according to either DNA-guided NGS or transcriptional analysis, specifically comparing tumor to matched normal tissue. This study successfully guided 35% of patients (n = 107) (69 patients DNA guided (64.5%) and 38 patients RNA guided (35.5%)) with refractory cancers to a therapeutic agent and demonstrated the utility of transcriptomics in exposing otherwise unspecified avenues of therapy. Overall efficacy between transcriptome-matched drugs and genotype-matched drugs was similar with response rates ranging between 20 and 30%.

Epigenomics

Epigenomics can be defined by the genome-wide identification of chemical modifications such as methylation and acetylation of DNA and/or DNA-binding histone proteins. Alterations in epigenetic mechanisms have been implicated in numerous malignancies including HNSCC, and represent an active area of research [66, 67]. Epigenetic changes have been recognised as fundamental mechanisms for carcinogenesis, and may have a role in early detection, treatment, and prognostic assessment for the cancer patients [66–72]. DNA methylation has become an increasingly attractive diagnostic biomarker that can be measured and evaluated with ctDNA.

Metabolomics

The field of metabolomics has garnered increasing attention in recent years, and there has been renewed interest in its role as a potential modulator of cancer

metabolism, which may further inform on phenotype [73]. Metabolomics is centred on the study of a metabolite within a system, and the levels of various metabolites can reveal an exclusive 'fingerprint' specific to that individual, providing information on the effect of gene/post-transcriptional regulation and altered pathway interactions [74]. Several studies have reported the role of tumor metabolism in cancer development and therapeutic response and resistance, and recently the role of glycolysis has come to the forefront [75–77]. Jiang et al. recently reported glycolytic activity was likely correlated with active immune signatures in various cancers, and highly glycolytic tumors presented an immune-stimulatory tumor microenvironment [78]. They found that glycolytic activity enhances PD-L1 expression on tumor cells and promotes anti-PD-1/PD-L1 immunotherapy response, suggesting a role as a potential predictive biomarker. Further, Cascone et al. identified tumor glycolysis as a pathway associated with immune resistance in melanoma [75]. In addition, new efforts have focused on identifying tumor-specific metabolite profiles including in HNSCC using different biological sample types and a variety of novel metabolomic platforms and technologies [79]. For example, the salivary metabolite profile has recently been shaped by the emerging knowledge of oral host–microbiome interactions.

Microbiome

The human body, particularly the oral cavity and gut, is host to rich and taxonomically diverse multi-species microbial communities. The microbiota typically exists in a symbiotic relationship with the host, regulating immune function and providing protection from pathogens. Disturbances in this intricate relationship, referred to as dysbiosis, often as a result of poor oral health or antibiotic use, may alter the community composition and induce inflammatory reactions, DNA damage and apoptosis. This results in altered metabolism and has subsequently been implicated in the pathogenesis of various malignancies including HNSCC [79–83]. In these patients chemoradiotherapy has recently been implicated in dysbiosis, where increases of potentially pathogenic species were found in patients with locally advanced oropharyngeal cancer [84]. Retrospective cohort studies have demonstrated varying microbiota composition in the saliva of HNSCC patients compared with healthy controls, while the presence of specific strains of bacteria has been associated with reduced risk of developing HNSCC [83, 85–88]. In the immuno-oncology setting differences in species population have been reported in both responders and non-responders. For example in melanoma patients whose baseline microbiota was enriched with *Faecalibacterium* genus and other Firmicutes showed a longer PFS and OS than those whose baseline microbiota was enriched with *Bacteroides* upon ipilimumab treatment [89]. Recent studies have also suggested that the immune microbiome plays a role in the development of toxicity [89–92]. Taken together the presence of specific bacterial strains may have the ability to modulate cancer progression and impact therapeutics [93]. As such metagenomic profiling and whole

genome shotgun sequencing of these microbial communities have become yet another increasingly attractive area of cancer research and precision medicine. Attempts to manipulate the gut microbiota to modulate the host immune response and further elucidate the mechanisms of response and toxicity are ongoing (NCT03686202, NCT03838601).

Artificial Intelligence/Radiomics

The field of artificial intelligence (AI) is also evolving and being incorporated into the clinical arena, particularly pertaining to the increasing use of immunotherapeutic agents and in the context of radiation therapy. Machine learning (ML) is an AI tool that can process enormous amounts of imported data, enabling classification with predictive capabilities, uncovering patterns that can predict outcomes with a high degree of accuracy. It has potential roles in cancer screening, diagnostics and prognostication; with a recent report demonstrating its ability to predict genotypes associated with poor prognosis in patients with lung cancer [94]. AI is also becoming an important decision support tool in the management of radiation oncology complications. Recently computational modelling has been shown to accurately predict two of the most challenging side effects associated with radiation therapy for head and neck cancer patients; weight loss and the need for feeding tube placement [95]. This AI precision oncology approach may thus have the potential to better identify patients who might benefit from early supportive interventions.

In HNSCC, radiomic efforts are currently concentrated on pathological classification and risk stratification of disease, aiming to prognosticate survival and predict response to treatment [96]. Several studies have demonstrated the potential in identifying clinically relevant molecular phenotypes such as HPV status, and the ability to determine histological diagnosis and stage of disease [96–99]. Models combining radiomic and clinical features have shown better accuracy in determining locoregional control and lymph node failure than either parameter independently, in both CT and MRI based studies [100–102]. In a study by Aerts et al., radiomic analysis of independent data sets from 1019 head and neck and lung cancer patients revealed a prognostic radiomic signature that was associated with intratumoral heterogeneity. This non-invasive, low-cost technique provides an opportunity for prognostic stratification of patients that may help guide treatment choice [103]. Quantitative analyses of available CT images of head and neck cancer patients have revealed a pattern of radiomic signatures that could be used to predict patterns of response and resistance to immune checkpoint inhibitors [104]. A retrospective radiomic response evaluation of recurrent/metastatic HNSCC patients treated with pembrolizumab within the KEYNOTE-012 study is ongoing, with tumor and peritumoral features of target lesions at baseline aiming to predict lesional level and overall response [105]. Successful modelling would allow for improved patient selection, increasing likelihood of response and reducing unnecessary toxicity and cost.

Although very much in its infancy, radiomics is a non-invasive 'omic' area that complements the advancement towards personalized cancer medicine. The limitations at this stage include heterogeneity in study methodology and statistical modelling, leading to challenges in comparison, reproducibility and validation of results [106]. As such the role in precision oncology remains uncertain and will require significant safeguards in place to reduce biases and allow meaningful translation into the clinic [107].

Conclusion

It is evident there has been tremendous advances in precision oncology in head and neck cancer in recent years. While this has largely been led by the field of cancer genomics, the increasing design and incorporation of innovative methodology and technology will continue to broaden the therapeutic scope for these patients. Increased understanding of the tumor microenvironment and host immunity will also advance precision immuno-oncology and the development of rational combination strategies. Despite these advances, sustained scientific collaboration remains paramount to realise the goal of precision medicine in HNSCC patients.

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