Exploiting molecular genomics in precision radiation oncology: a marriage of biological and physical precision

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Abstract: Achieving local tumour control is paramount for cure in head and neck and prostate cancers. With the transition to precision radiotherapy (RT) techniques, survival rates have improved in the majority of these cancers, but a substantial proportion of 30–40% still relapse following primary treatment. Recent large-scale molecular profiling studies have revealed unique biological events that could explain for tumour aggression and resistance to therapies, redefining the molecular taxonomy of head and neck and prostate cancers. Here, we reviewed the key findings from these studies, highlighting those relevant for clinical stratification. We also proposed novel combinatorial clinicomolecular models to identify subsets of patients with aggressive localised tumours and limited metastases, and to inform on the optimal management of these patients using molecular targeted agents, immunotherapy, and RT.

Keywords: Precision radiotherapy (precision RT); stereotactic radiotherapy (stereotactic RT); radiosurgery; molecular biomarker; genomics; prognostic; predictive

Introduction

Advances in radiation delivery in the last decade have driven substantial improvement in physical precision of radiotherapy (RT) targeting of tumours. With intensity modulated radiotherapy (IMRT), there is now the ability to shape deposition of radiation doses around concave contours, thereby ensuring dose intensity to the tumour while limiting exposure of adjacent normal tissues. Likewise, image guided radiotherapy (IGRT) with daily cone beam imaging has added another layer of physical precision. Both technologies are culpable for the enhanced therapeutic ratio of RT; clinical evidence from prospective trials and observational audits have indicated significant improvements in disease control, survival, and reduction of normal tissue complications (1,2).

More recently, proton therapy has been proposed as an even more superior technology for RT delivery through exploiting the Bragg’s peak characteristics of the proton beam; this yields the theoretical advantage of focused dose intensity at the tumour, while further limiting the exposure to normal tissues due to the sharp dose fall-off. It is through the advent of these advanced technologies that has partly motivated the design of RT fractionation schemes that are intended to achieve “tumour ablation”; these regimes exploit the incremental biological effects of large doses per RT fraction in tumours like prostate and breast cancers that are intrinsically sensitive to fraction size variation (3,4). Clinical evidence supporting the efficacy of such stereotactic ablative (radiosurgical) regimes is being presented by several accompanying reviews in this Chinese Journal of Clinical Oncology Special Issue.
Nonetheless, against the background of technological advances, it is arguable that recent clinical gains from improved physical precision have been less impressive. For example, comparisons of clinical outcomes of patient cohorts who had been treated with either proton therapy or IMRT have not been conclusively in favour of protons (5-8). It is therefore plausible to consider that subsequent therapeutic strategies will require a marriage of physical and biological precision in order to achieve the next substantial gain in precision radiation oncology. It is also coincidental that simultaneous with the progress in RT technologies, there are now high throughput next generation sequencing (NGS) techniques that have improved the efficiency and quality of molecular profiling of human tissues. This has led to the generation of robust datasets on molecular taxonomies of several human cancers by large collaborative consortiums like the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) (9-12). Apart from providing a molecular taxonomy on individual cancers (thereby prompting the revisit of our conventional approach of clinical stratification by the TNM stage classification system), other insights gained from these molecular profiling studies include discovery of novel driver mutations that are biomarkers of adverse prognosis and therapeutic resistance. The latter would imply a predictive biomarker that is potentially ‘druggable’ for synergism with standard therapies to counter clonal resistance and tumour recurrence (13,14). This review thus aims to discuss the scientific rationales and considerations underpinning various precision RT strategies, with specific focus on head and neck and prostate cancers. Here, we will first review the current literature on the molecular landscape of these cancers; next, we will discuss the clinical relevance of the molecular features; finally, we will suggest possible approaches of incorporating matched tumour and germline molecular profiling in designing precision RT strategies in the treatment of these cancers.

**Search strategy**

We searched the PubMed and MEDLINE databases for articles published in English from 01 January 2000 to 30 December 2016 with the keywords ‘molecular’, ‘genomics’, ‘epigenomics’, ‘biomarkers’, ‘prognostic’, ‘predictive’, ‘radiation’, ‘radioresistance’, ‘head and neck’, ‘prostate’, ‘cancers’, ‘carcinoma’, ‘radiotherapy’, ‘radiosurgery’, ‘stereotactic body radiotherapy’, and ‘ablative therapy’. Articles were selected based on relevance, with priority given to highly-cited articles, and articles written in English. Conference abstracts were also reviewed, and considered if they reported statistical methods and hazard ratios (HR), with corresponding confidence intervals (CI) and P values. Articles that preceded the search time-frame were also included if they were highly regarded seminal work.

**Molecular characterisation of head and neck and prostate cancers**

Epidermal growth factor receptor (EGFR) amplification was among the initial oncogenic driver events that were characterised in head and neck squamous cell cancer (HNSCC) (15-17). As shown by Ang et al. and several others, overexpression of EGFR was common in these tumours, and importantly, predicted for inferior locoregional tumour control following primary RT. Targeting of this receptor through anti-EGFR antibody (cetuximab) was able to inhibit the molecular processes contributing to tumour aggression, thereby improving clinical outcomes in patients treated with combination cetuximab-RT (18). However, More recently there is an emergence of a new phenotype of HNSCC that is associated with human papillomavirus (HPV) infection (19-21). From large-scale epidemiological studies, it was observed that while different HPV-serotypes (-16, -18, and others) have been implicated in head and neck carcinogenesis, oncogenic potential differed between the serotypes, and there is a tropism of HPV to the oropharynx, albeit HPV has also been detected in other head and neck anatomical sub-sites. Of note, the association is strongest between HPV-16 infection and the onset of oropharynx squamous cell carcinoma (OPSCC); it is also in HPV+ OPSCC where these patients have a distinctly more favourable prognosis compared to HPV+ HNSCC of other sites and HPV− HNSCC (22,23). While the oncogenic potential of HPV-16 can be attributed to the expression of E6 and E7 proteins, which are known to inhibit TP53 and RB1, respectively, the mechanistic bases underpinning the favourable prognosis and optimal response of HPV+ OPSCC to RT are less definitive. Disruption of cell cycle checkpoint mechanisms, DNA repair and damage responses have been proposed to account for the increased radiosensitivity of these tumours (24). In the landmark report by TCGA on 279 HNSCCs, it was observed that specific mutational events may be enriched in HPV+ and HPV− HNSCC (activated PIK3CA (56% vs. 34%) and FGFR3 (11% vs. 2%), loss
of TRAF3 (22% vs. 1%) in HPV+ tumours; EGFR, FGFR1, CCND1, CDK6, MYC, IGFR1, FAT1 in HPV- tumours). However, these events alone do not fully explain the discordant natural histories of these tumours (12). Other common events such as inactivating mutations in NOTCH1 were also observed, regardless of HPV status, which hints at a novel function of NOTCH1 as a tumour suppressor rather than an oncogene in HNSCC (12,25,26). From a broader genome-wide perspective, intra-tumoral and inter-individual molecular heterogeneity of HNSCC were also appreciable from these landmark sequencing studies, and add prognostic information to conventional clinical indices (27).

Unlike HNSCC, the majority of localised prostate cancers harbour a paucity of somatic nucleotide variants (SNVs); in an analysis of 200 whole genome shotgun (WGS) and 277 whole exome sequences (WES), Fraser et al. reported SNV frequencies of less than 10% for SPOP, MED12, TP53, FOXA1 in non-indolent prostate cancers with similar clinical risk profiles (28). Rather, the molecular taxonomy of localised prostate cancers is better defined by copy number aberrations (CNA), structural chromosomal hypermutations (chromothripsis and kataegis) and rearrangements. In particular, Lalonde et al. showed that localised prostate cancers could be classified by global CNA and gene rearrangement profiles into four subclasses, independent of Gleason’s score (GS) (29). The significant intra-tumoral spatial genomic heterogeneity further highlights the biological complexity of multifocal prostate cancers that could not be discerned by conventional GS and histomorphology (30,31). Beyond the variation in global CNA profiles, prostate cancers are also prone to recurrent gene-specific CNAs such as amplification in MYC, and losses in PTEN, RB1, TP53, CHD1, CDH1, and NF2 (32). Among recurrent gene rearrangements, TMEM106B: ERG somatic fusion is most common, occurring in 50% of prostate cancers. Nonetheless, novel inversions also have been reported; Fraser et al. described a recurrent inversion at the PTEN gene locus affecting downstream gene expression (28). In a separate cohort of NCCN-defined high-risk advanced tumours, Baca et al. presented a novel concept of “chromoplexy”, whereby inter-dependent DNA translocations and deletions occur to dysregulate prostate cancer genes in a coordinated manner (33). Finally, the tumour microenvironment within the prostate gland is also prone to effects of hypoxia and co-occurrence of subpathologies such as intraductal and cribriform variants, which raises the possibility of interdependency between the intrinsic tumour molecular characteristics and the surrounding microenvironment (34,35). Taken together, the findings of these studies have provided us with a profound insight on several novel biology in these and other human cancers, in hope that we can eventually link these molecular indices to tumour aggression and therapeutic resistance.

**Clinical relevance of somatic and germline mutations in HNSCC and prostate cancers**

Treatment recommendation of HNSCC is largely based on a risk-adapted approach using conventional clinical indices; early stage disease (TNM stages I and II) is typically managed with either surgery or RT, while locally advanced tumours (TNM stages III and IV) are treated with either definitive chemoRT or surgery followed by adjuvant therapies (RT or chemoRT). Nonetheless, clinical stratification for personalised treatment strategies can be achieved with incorporation of molecular indices. An illustrative example will be overexpression of EGFR and HER2, which are known adverse prognostic biomarkers in this disease, and targeted therapeutics such as cetuximab and gefitinib are effective in “drugging” this activated pathway in HNSCC. Although modest response rates of 15–20% to either agents in unselected patient populations have been reported (36,37), presence of a germline mutation in KRAS may be predictive of cetuximab efficacy [HR for overall survival (OS) =0.19, P=0.03; progression-free survival (PFS) =0.31, P=0.04 in favour of KRAS-variant] (38). Separately, tumours eventually acquire resistance to these agents through co-occurrence of other gene alterations in ERBB2, MET, PIK3CA, PTEN and HRAS (12). Detailed characterisation of molecular pathways that are aberrant prior to and at the point of resistance would thus provide the scientific rationales of novel combinatorial targeted therapeutic regimes.

Assessment of HPV status by immunohistochemical staining of its surrogate marker—p16 and/or HPV RNA in situ hybridisation (ISH) is routine at present when performing histopathological analysis of HNSCCs, even though information on prognosis is primarily limited to OPSCC (23). Batran et al. further suggested that prognostication power varies between HPV-serotypes; in their analysis of 73 HPV+ tumours from the TCGA cohort, they observed that HPV-16 was associated with superior survival when compared to HPV-other serotypes (39). Nonetheless, it is conclusive that the strength of HPV as a
More recently, mutations in DNA repair genes have also been implicated in the development of aggressive prostate cancer and response to targeted therapeutics; a prime example is the anti-tumour activity with inhibition of PARP1 in metastatic prostate cancers harbouring germline and somatic mutations in DNA repair genes, particularly in those involved in homologous recombination (53,54). Interestingly, germline mutations in DNA repair genes were also more frequent among patients with aggressive metastatic disease compared to their indolent counterpart (11.8% vs. 4.6%), with BRCA2 (5.3%) being the most frequent aberration (54). These findings justify the approach of molecular profiling of paired prostate tumour-normal tissues, in order to determine the optimal therapeutic strategy for the individual patient (Table 1) (55-65).

Optimising RT therapeutic ratio: germline genetic predictors of normal tissue toxicities

Apart from inter-individual heterogeneity in tumour response to RT, a wide variation also exists in normal tissue RT-response between non-syndromic individuals, which are unexplained by clinical and treatment parameters (66,67). It is estimated that up to 60% of inter-individual heterogeneity in normal tissue RT-sensitivity may be due to intrinsic genetic susceptibility, likely influenced by low penetrance allelic variation (68). Identifying genetic signatures of normal tissue RT-sensitivity could therefore offer another paradigm of precision RT; de-escalating RT doses in individuals assessed to be RT-sensitive (by signature) and intensifying treatment in patients who are determined to be less prone to RT-induced normal tissue toxicities. There are now several genome-wide association studies (GWAS) that have investigated for predictive single nucleotide polymorphism (SNP)-based signatures of specific RT-induced normal tissue end-points: Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy (RAPPER), RADIOGEN, Gene-PARE and Cross Cancer Institute (CCI) (69-73) (Table 2); notably, SNPs in TANC1 and XRCC1 have been reported to predict for erectile dysfunction and breast fibrosis, respectively (71,72). While we await validation in larger cohorts (73,74), other assays including radiation-induced lymphocyte apoptosis (RILA) have been prospectively validated to predict for severe reactions following breast RT (75,76). Going forward, it is plausible to consider a clinical pathway that personalises RT doses for each patient based on profiling data of matched tumour and normal tissue RT-sensitivity in the same patient.
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Tumour biomarker</th>
<th>Type of genetic aberration/SNP (frequency) (%)</th>
<th>Prognostic/predictive</th>
<th>Targeted therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>TP53 (55,56)</td>
<td>Mutation (74.0)</td>
<td>Prognostic, predictive</td>
<td>WEE-1 kinase inhibitor</td>
</tr>
<tr>
<td></td>
<td>CCND1 (57)</td>
<td>Amplification (27.6)</td>
<td>Predictive</td>
<td>CDK inhibitor (e.g., ribociclib and palbociclib)</td>
</tr>
<tr>
<td></td>
<td>EGFR (18,58)</td>
<td>Amplification (10.8)</td>
<td>Prognostic, predictive</td>
<td>Predicts for benefit from cetuximab-RT</td>
</tr>
<tr>
<td></td>
<td>HER2 (59)</td>
<td>Amplification (2.2), mutation (1.8)</td>
<td>Predictive</td>
<td>Predicts for response to cetuximab and gefitinib but tumor eventually acquire resistance</td>
</tr>
<tr>
<td></td>
<td>KRAS (38)</td>
<td>Germline (0.1)</td>
<td>Predictive</td>
<td>Predicts for benefit from cetuximab-RT</td>
</tr>
<tr>
<td></td>
<td>HPV (21,60,61)</td>
<td>Present in 63.8% (White Caucasians)</td>
<td>Prognostic, predictive</td>
<td>RT dose de-escalation in HPV + OPSCC; Nimorazole-RT in HPV-OPSCC</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>CMYC (62)</td>
<td>Amplification (7.2)</td>
<td>Prognostic</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>SCHLAP1 (49,50)</td>
<td>Overexpression (9.5)</td>
<td>Prognostic</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Genomic instability (29,48)</td>
<td>100-, 31-loci signature</td>
<td>Prognostic</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Localised somatic hypermutations (28)</td>
<td>Chromothripsis (20.0), kataegis (23.0)</td>
<td>Prognostic</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Recurrent gene rearrangements (28)</td>
<td>TMPRSS2: ERG rearrangement (40.0–50.0)</td>
<td>Prognostic</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PTEN (28)</td>
<td>Novel inversion, deletion</td>
<td>Prognostic</td>
<td>–</td>
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<td></td>
<td>Hypoxia (29,34)</td>
<td>–</td>
<td>Prognostic, predictive</td>
<td>Nimorazole and other hypoxic modifiers</td>
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<tr>
<td></td>
<td>BRCA2 and other DNA repair genes (63,64)</td>
<td>Deletion (0.6)</td>
<td>Prognostic, predictive</td>
<td>Predict for response to PARP inhibition</td>
</tr>
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<td></td>
<td>NBN (65)</td>
<td>Amplification (6.0)</td>
<td>Prognostic, predictive</td>
<td>Predicts for radioresistance</td>
</tr>
<tr>
<td></td>
<td>HSD3B1 (51)</td>
<td>Germline (0.3)</td>
<td>Predictive</td>
<td>Predicts for sensitivity to androgen suppression</td>
</tr>
</tbody>
</table>
Designing biomarker-directed therapeutic strategies in head and neck and prostate cancers

Given the RT-sensitivity and favourable prognosis of HPV+ OPSCC, the feasibility of RT dose de-escalation were formally tested in small single-arm phase II studies, with encouraging preliminary results (77). In two of the studies that have been reported, response to induction chemotherapy was employed as a method of stratifying patients to a lower RT dose of 54 Gy, while simultaneously targeting occult metastases with the upfront administration of systemic therapy (43,44). While the systemic therapy regimes varied in both studies (three cycles of induction cisplatin, paclitaxel, cetuximab and concurrent cetuximab in ECOG 1308; two cycles of induction carboplatin, paclitaxel and concurrent paclitaxel in the UCLA trial), the study investigators reported 2-year PFS of 80% and 92%, respectively.

Treatment intensification strategies in HPV− HNSCC have included testing the efficacy of combination hypoxia modifiers (nimorazole, tirapazamine) and RT, with the aim of sensitising radioresistant hypoxic clones in these tumours. The background to this strategy was in part based on a post-hoc analysis of p16 expression as a surrogate for HPV-status in the DAHANCA-5 randomised controlled phase III trial of nimorazole-RT compared to RT alone (78); the study investigators observed that negative expression of p16 was predictive of nimorazole efficacy (HR of loco-regional failure with nimorazole 0.69, p16− vs. 0.93, p16+) (79). This strategy is currently being formally investigated in a randomised controlled phase III trial (ClinicalTrials.gov, NCT01880359) (80). Another rationale for treatment intensification in this adverse subgroup involves the targeting of occult metastases. To this end, investigators have examined the role of maintenance afatinib (an EGFR and HER2 tyrosine kinase inhibitor) following chemo-RT in two large randomised studies (LUX-2 and LUX-4), both of which unfortunately failed to demonstrate an efficacy of the targeted agent in this setting (81). Novel regimes are therefore needed, and we await the results of ongoing immunotherapy trials [ClinicalTrials.gov, NCT02952586 (JAVELIN), NCT02777385, NCT02764593 (RTOG 3504)].

A similar approach could also be applied in the treatment of localised prostate cancer; while most tumours are indolent in nature, and could be considered for single modality surgery or RT without dose escalation, those...
harbouring aggressive features of SChLAP1 expression and genomic instability ought to be considered for treatment intensification with second generation anti-androgen therapies (enzalutamide and abiraterone). In addition, biomarkers that are predictive of RT- (NBN amplification) and androgen-sensitivity (HSD3B1 variant) could also be incorporated into a clinical decision making tool comprising of combinatorial clinical indices and prognostic biomarkers; for example, in individuals with prostate tumours harbouring a constellation of hypoxia, subpathologies, and genomic instability (46), these men should be referred for treatment intensification clinical trial protocols, which could embed additional stratification measures to (I) surgery or RT based on an RT-sensitivity signature, and (II) chemotherapy or hormonal therapy for targeting systemic disease depending on their germline HSD3B1 status (Figure 1). In the metastatic setting, germline and tumour sequencing should be performed, since this could help direct patients to treatment with PARP1 inhibitors (olaparib, etc.) in the presence of mutations in DNA repair genes (53). Nonetheless, there are several caveats with such precision approaches. Foremost, large-scale prospective validation is required for several of these molecular biomarkers to verify the magnitude of association with clinical outcomes. Next, standardisation of the molecular assays to achieve robust reproducibility and reliability is paramount to ensuring consistency of the assay read-out across multiple centres. Lastly, a challenge yet to be adequately addressed relates to the impact of intratumoral heterogeneity on the accuracy of genotype-phenotype (82), and if liquid biopsies represent the solution to more invasive and costlier multiregional tumour sampling.

**Figure 1** Illustrative example of a personalised management strategy based on combinatorial prognostic and predictive biomarkers in men with localised prostate cancers.

**Combinatorial approach of precision molecular profiling and ablative stereotactic RT**

While the role of stereotactic body RT (SBRT) or radiosurgery (SRS) was initially intended for optimisation of symptom palliation, there is an emerging concept among clinicians to exploit SBRT and SRS in targeting isolated metastases, such that these patients harbouring a “low” burden of systemic metastases are potentially “cured” if the metastatic tumour clones are eradicated. Supportive evidence for such a disease state can be drawn from clinical examples in colorectal, renal, and soft tissue cancers (83). Nonetheless, current methods of stratifying for these favourable patients are imprecise, and do not incorporate indices indicative of tumour biology; they often rely on assessment for (I) number of metastatic lesions; (II) sites of metastasis; (III) disease-free interval; and (IV) control of primary disease. In this instance, one could identify the relevance of a molecular signature for an oligometastatic state, which would enhance our ability to identify patients with truly limited disease. Of note, liquid biopsies that rely on quantification and characterisation of circulating tumour cells (CTCs) and cell-free tumour DNA (cfDNA) could fulfil this clinical purpose, and have demonstrated preliminary success in early-stage colorectal and lung
cancers (84,85). In the larger TRAcking Cancer Evolution through therapy (Rx) (TRACERx) study, Abbosh et al. reported on a novel technology that could detect cfDNA in 100 early-stage lung cancer patients, coupled with a high fidelity in phylogenetic analyses to track clonal evolution that could predict resistance to adjuvant chemotherapy and risk of recurrence (84). Separately, Tie and colleagues demonstrated that detection of tumour-associated mutations in cfDNA was predictive of a benefit with adjuvant chemotherapy in patients with stage 2 colorectal cancer following surgery (85). Based on these examples, it is plausible to consider the utility of this technology for a more accurate stratification of patients with oligometastatic disease, who would be ideal candidates for more aggressive intervention.

Precision molecular profiling could also be useful for evaluating tumour immunogenicity. As discussed elegantly in the companion review article by Tharmalingam and Hoskin (86), there is good level of evidence that innate and adaptive anti-tumour immune responses are triggered by RT, and RT-induced immunogenic cell death (ICD) is particularly dominant at large fraction sizes (87). Moreover, the synergism that is observed with combining RT and immune checkpoint inhibitors [anti-programmed cell death-1 (PD1) and ligand-1 (PDL-1)], anti-cytotoxic T lymphocyte-associated protein-4 (CTLA4) supports ICD as a main mechanism of SBRT and SRS anti-tumour efficacy (88). ICD can be exerted through an acute release of tumour-associated antigens release leading to priming of cytotoxic T-cells, and recruitment of antigen presenting cells (APC) and dendritic cells (89). Therefore, profiling of tumour mutational burden and the immune microenvironment ought to be performed in ongoing trials of combination immuno-RT, in order to derive potential predictive signatures. The above outlined concepts are illustrated in Figure 2.

**Conclusions**

In the past decade, the radiation oncology community has embraced the technological advances that have transitioned the field into an era of precision RT, which have not only contributed to tremendous gains in tumour control probability and reduction of normal tissue toxicities, but in the same vein, catered for novel tumour ablative treatments. Consequently, we have witnessed some practice-changing transitions in cancer management; examples include the safe delivery of prostate RT in five fractions over two weeks as opposed to two months of conventionally fractionated RT, and the ablation of oligometastasis resulting in curing of patients with disseminated disease. These are landmark improvements in patient survivorship and quality of life. That said, we argue that the next wave of therapeutic gains will come from biological precision strategies. Here,
we presented data on our current understanding into the molecular drivers of carcinogenesis, tumour aggression, and treatment resistance in HNSCC and prostate cancer. We reported on how some of these molecular indices have the potential utility in patient prognostication and influencing treatment recommendation. As we deepen our scientific understanding, it is only imaginable that individualised prescription of RT doses and combination regimes will become a reality in due course.

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Footnote

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

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