

Nasopharyngeal carcinoma—past lessons and a glimpse into the future

Nasopharyngeal carcinoma is a unique cancer with specific patterns of racial and geographical distribution, which may be linked to demographic-specific genetic susceptibility and viral-induced tumorigenesis by Epstein-barr virus (EBV) and human papilloma virus (HPV) (1). Over the recent decade, incidences of nasopharyngeal carcinoma are gradually declining, in part due to large-scale public health intervention programs in endemic regions of Southern and Eastern Asia. Curability of this disease across all tumour stages has also improved remarkably (2). It is therefore fitting that the *Chinese Clinical Oncology* chose to dedicate a special issue on nasopharyngeal carcinoma, which is intended to review current insights into tumour biology, and highlight past, present, and future clinical advances.

Epidemiological studies have identified lifestyle and dietary risk factors that could contribute to the development of nasopharyngeal carcinoma. However, in recent times, genome-wide association studies (GWAS) to identify genomic linkages with human diseases are made possible due to the advent of high throughput next-generation sequencing. Bei *et al.* in their review, provided an update on the findings of past GWAS on nasopharyngeal carcinoma, and highlighted ongoing efforts (3). In the same vein, Dai *et al.* and Spence *et al.* discussed the molecular profiling studies in nasopharyngeal carcinoma that have led to the discovery of driver mutational events, which are embedded in the genomic coding and non-coding regions, and the methylome (4,5). Collectively, these articles provide a comprehensive overview of the scientific discoveries in tumorigenesis and disease progression in nasopharyngeal carcinoma.

Multiple factors have led to the substantial improvement in clinical outcomes of nasopharyngeal carcinoma patients; they include better patient stratification, modern imaging and radiotherapy techniques, the conduct of several randomized controlled trials on the combination of chemotherapy with radiotherapy, and the discovery of novel agents against metastatic disease. Zong *et al.* discussed the Chinese staging system of nasopharyngeal carcinoma, which is distinct but not mutually exclusive to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) stage classification (6). The same group had also recently proposed changes to the 8th edition of the AJCC/UICC staging system, and it may be that both the Chinese and AJCC/UICC staging systems will be eventually integrated (7). Apart from stage classifications, EBV DNA has also emerged as a complementary biomarker for disease prognostication, and the clinical utility of this test is reviewed by Fung *et al.* (8). Contemporary imaging techniques, such as functional imaging with hypoxia markers, can also inform about tumour biology, as described by Yip *et al.* (9). With these advances, it is to be expected that future patient stratification will likely be based on a combinatorial scheme of functional imaging, molecular biomarkers, and conventional stage classification.

Another frontier of advancement relates to modern radiotherapy techniques and novel systemic agents. Where available, intensity modulated radiotherapy is the preferred choice of radiation delivery, yielding better tumour control and toxicity outcomes. However, the achievement of better cure rates inevitably raises concerns of survivorship issues. It is therefore appropriate that Yom *et al.* reviewed existing measures that are intended to address radiotherapy-associated morbidities, and their corresponding levels of effectiveness.

Proton therapy, with its superior dosimetric profile over photons, represents another major development in the field of radiotherapy. However, there is limited experience with proton therapy worldwide, and thus Holliday *et al.* reported on the existing evidence, and shared their local experience at the MD Anderson Cancer Centre (10). Besides its potential therapeutic advantages in advanced disease, proton therapy is perhaps even more ideal for targeting radioresistant locally recurrent disease, as reviewed by Kong *et al.* (11). These reviews constitute a timely prelude to the much anticipated results of ongoing clinical trials on proton therapy.

Concurrent chemo-radiotherapy and combinational chemotherapy regimens have both contributed to substantial improvements in survival rates of patients with advanced and metastatic disease, respectively. Xu *et al.* provided a comprehensive review of past and ongoing clinical trials of combination chemotherapy in the advanced setting, while Tan *et al.* described the novel systemic regimes in patients with metastatic disease (12,13). Separately, immunotherapy has come forth in the past year as a major discovery in the treatment of several solid tumours. Likewise in nasopharyngeal carcinoma,

vaccine-based immunotherapy has been in testing for nearly a decade. Taylor *et al.* and Jain *et al.* presented the scientific rationales and evidence supporting the efficacies of vaccine-based tumour antigen-specific immunotherapy, as well as modern antibody-based immunotherapy that targets common immune checkpoint pathways (14,15). Taylor *et al.* further examined why past strategies might have yielded suboptimal results, and proposed new ways of incorporating vaccines to conventional treatment modalities, particularly in the non-metastatic setting (14).

Finally, we solicited reviews that offered a global perspective on the outcomes of nasopharyngeal carcinoma patients from parts of the world with low- to middle-income, and where this disease is less prevalent. Lam *et al.* reported on the suboptimal outcomes of nasopharyngeal carcinoma patients from the impoverished regions, and narrated an IAEA initiative to target this issue (16). With the relatively low prevalence of nasopharyngeal carcinoma in South Korea, Ahn *et al.* reported on the experience of the Korean Radiation Oncology Group in creating a nation-wide database, capturing patterns of care and survival outcomes (17). This should serve as an inspiration to the rest of the medical community that meaningful outcomes are best achieved through collaborations, rather than allow the lack of patient numbers handicap our goals of improving patient outcomes.

To conclude, we offered some comments on the tumorigenesis of nasopharyngeal carcinoma, and the roles of adjuvant chemotherapy and spatially fractionated GRID radiotherapy in the treatment of locally advanced disease (18). The carefully chosen articles in this special issue present the multi-faceted transition in the understanding and management of nasopharyngeal carcinoma. We trust that readers will find them highly informative.

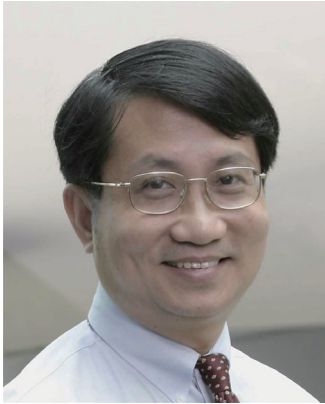
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