Beating 'Guangdong cancer': a review and update on nasopharyngeal cancer

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A B S T R A C T

Once endemic in southern China, nasopharyngeal cancer is becoming less prevalent in Hong Kong. This is probably due to a better understanding of the risk factors associated with the disease, its genomic landscape, advances in radiotherapy technology, and development of effective systemic agents. More specifically, the close relationship between Epstein-Barr virus and nasopharyngeal cancer opens up the possibility of using Epstein-Barr virus DNA as a biomarker for early detection and monitoring of the disease. On the other hand, the looming genomic data for nasopharyngeal cancer aid in the development of powerful biomarkers and promising targeted therapy. Clinical use of a combination of radiotherapy and chemotherapy continues to increase, while the development of immunotherapy, such as checkpoint inhibitors, offers hope in improving treatment outcome.

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Introduction

Nasopharyngeal cancer (NPC) was once considered endemic in the southern part of China. This type of cancer was so prevalent in Guangdong Province in southern China in the early 20th century that it was dubbed 'Guangdong cancer'.[1] Although the name is now less popular and the incidence of NPC has been decreasing since then (Fig),[2,3] its occurrence in Hong Kong and Southeast Asia is still considerably higher than in other parts of the world: the age-standardised incidence rate was 7.9 per 100 000 population in 2014 in Hong Kong,[3] compared with less than 1.0 per 100 000 population in North America and Europe.[4] The global data from GLOBOCAN in 2012 showed that 38% of all new cases of NPC were registered in China.[5]

While Hong Kong is one of the regions that experience the most NPC,[6] it has also become a centre for NPC research. Indeed, many important and landmark studies in NPC were performed in Hong Kong, where local experts have been responsible for developing practice guidelines with regard to the diagnosis, management, and follow-up of NPC.[7,8] It is thus interesting to review the updated knowledge about the aetiology, risk factors, diagnosis, and treatment strategies of this 'Guangdong cancer'.

Classification, aetiology, and risk factors

Classification and staging

Nasopharyngeal cancer can be categorised according to its histopathology: keratinising, non-keratinising (which can be further subdivided into differentiated and undifferentiated forms), and basaloid squamous cell carcinoma; all of which are to replace the old numerical classification system.[9] In endemic regions such as Hong Kong, non-keratinising carcinoma predominates, whereas the keratinising type is more common in other parts of the world.[10]

Nasopharyngeal cancer is staged according to the tumour, node, metastasis system. To assist with the prognosis and guide treatment decisions, NPC can be further stratified into five different stages (stages I, II, III, IVA, and IVB), as suggested by the latest American Joint Committee on Cancer (8th edition) cancer staging manual.[11]

Viral factors

While it is widely believed that NPC is caused by the interaction of several factors, Epstein-Barr virus (EBV) infection is undoubtedly the most studied aetiological factor for NPC. This virus—as a primary aetiological agent of NPC, specifically the endemic non-keratinising type—has been supported by a large body of evidence[12]; a review in 2012 suggested that EBV accounted for more than 85% of NPC cases globally.[13] Based on in-situ hybridisation techniques[10] and the fact that EBV infects more than 90% of the population,[14] EBV reactivation is considered necessary in the pathogenesis of NPC; inhibition of EBV reactivation is currently being investigated as a possible approach to preventing NPC relapse.[15] What triggers the reactivation, however, is less well-defined, although cigarette smoking is among the possible reactivating factors.[16,17]

On the other hand, human papillomavirus (HPV), a common aetiological agent causing cervical cancer, is associated with the non-endemic, keratinising type of NPC, although evidence is

對付「廣東癌」：鼻咽癌的回顧與更新

何卓生

鼻咽癌於中國南部等地曾經令人聞之色變。隨著我們更瞭解鼻咽癌的風險因素、基因圖譜，以及更有效的治療方法，近年發病率呈下降趨勢。當中，艾伯斯坦－巴爾病毒（EBV）與鼻咽癌的密切關係為EBV脫氧核糖核酸的臨床應用打開了大門，例如早期篩檢和病情監察。鼻咽癌的基因數據則有助研究相關生物指標和標靶治療藥物的發展。治療方面，放射治療和化療的組合治療於臨床上的應用日趨常見，而免疫療法的面世則為治療帶來了新希望。

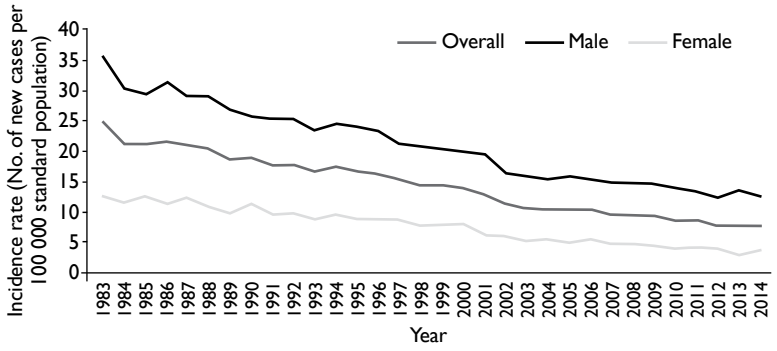

FIG. Age-standardised incidence rate of nasopharyngeal cancer by sex from 1983 to 2014[2,3]

limited due to its low prevalence.[18] While EBV and HPV infections are nearly always mutually exclusive in the pathogenesis of NPC,[9] studies have suggested that HPV-positive NPC is associated with poorer outcome when compared with EBV-positive NPC.[19]

Genetic factors

Genetic susceptibility has attracted intense interest since the development of various genomic techniques. A whole-exome sequencing study in 2014 revealed the genetic alterations that affect a number of cellular pathways, including chromatin modification, ErbB-phosphatidylinositol-3 kinase signalling, and autophagy machinery in NPC.[20] Epigenetic alterations of various chromosomal regions, especially those regions with tumour-suppressor genes, were also found in NPC patients.[21] Li et al[22] recently identified genomic aberrations of multiple negative regulators of the nuclear factor-κB (NF-κB) pathway in 111 EBV-positive NPC samples in another whole-exome sequencing study, suggesting the pivotal role of activating the NF-κB signalling pathway in NPC and the potential therapeutic applications of NF-κB inhibitors.[22] The researchers also revealed major histocompatibility complex class I gene aberrations in some of the samples, and the efficacy of immune checkpoint inhibitors (discussed below) may be affected in this subgroup of NPC patients.[22] Although much in this field remains to be elucidated, it is expected that the genetic research will aid in the development of powerful biomarkers for the diagnosis, prognosis, and evaluation of the treatment for NPC.[21]

Environmental factors

An increased risk of NPC has been associated with a number of lifestyle factors, among which a history of salted fish consumption has the strongest association. Various studies have confirmed its association with NPC,[23,24] and its relationship with the high prevalence of NPC in Hong Kong and neighbouring regions in the 20th century.[6] N-nitrosamine found in the preserved salted fish is believed to be the carcinogen concerned.[25] Other factors such as the use of Chinese medicinal herbs and high consumption of fermented food were also suggested, but the associations were often inconsistent among studies.[24]

Diagnosis

Nasendoscopy for a biopsy sample is essential for a definitive diagnosis of NPC. Detecting and diagnosing NPC at an early stage is of paramount importance: the disease stage is significantly correlated with the outcome in NPC, and early diagnosis may improve outcomes.[12] Cell-free EBV DNA analysis was shown to have high sensitivity and specificity in detecting NPC, and has been further validated by various studies.[26] A local study further showed that the analysis was useful in detecting early-stage NPC in asymptomatic individuals.[27] An expanded phase II study involving over 20 000 participants to evaluate its feasibility as a screening tool (NCT02063399) has just been completed, showing excellent sensitivity and specificity (97.1% and 98.6%, respectively).[28] Participants who were identified with NPC by this screening tool were detected significantly earlier and with better outcome when compared with those in a historical control.[28]

Other roles of Epstein-Barr virus DNA

With the substantial involvement of EBV in the pathogenesis of NPC, it is sensible to exploit EBV DNA as a biomarker in managing patients with NPC. One such application is the prediction of disease recurrence after treatment. Post-treatment EBV DNA level has been shown to be the most powerful predictor for disease recurrence and long-term survival in NPC patients of different ethnic origins, clinical stages, and treatment modalities.[29-36] Recently Lee et al[37] demonstrated that serial post–intensity modulated radiation therapy (IMRT) undetectable plasma EBV DNA was prognostic of all predefined survival end-points at 3 years in the modern IMRT era. Leung et al[38] further showed that detectable plasma

EBV DNA level at midcourse of radiotherapy (RT) or chemoradiotherapy (CRT) is adversely associated with worse overall survival (OS) and progression-free survival (PFS). This suggests the possibility of shifting prognostication from a post-therapy time-point to midcourse of therapy, and selecting high-risk patients for therapy intensification by measuring midcourse plasma EBV DNA level.[38]

Another notable application is the prediction of treatment outcome by measuring the clearance rate of plasma EBV DNA. Following the observation that EBV DNA was rapidly cleared from the circulation after surgical resection of NPC,[39] subsequent studies demonstrated that patients with more rapid clearance of plasma EBV DNA responded better to chemotherapy or CRT compared with patients with a slower clearance.[40,41] A prospective trial evaluating the response to chemotherapy by measuring plasma EBV DNA half-life together with tumour metabolic response (via fluorodeoxyglucose positron emission tomographic scan) is currently underway.

Treatment strategies

Radiotherapy

Radiotherapy has long been regarded as the mainstay of NPC treatment, due to the radiosensitive nature of the tumour, and the anatomical position of NPC that limits a surgical approach.[10] Of note, IMRT is currently the preferred approach, with its improved OS and decreased toxicity,[42] advantages in preserving parotid function and reducing severe xerostomia,[43] and improved quality of life compared with conventional two-dimensional (2D) RT.[44] It is currently used as a monotherapy for the early stage of NPC.

Since the pre-IMRT era, re-irradiation has been shown to be effective in non-metastatic, recurrent NPC (rNPC) patients after primary RT.[45-47] With its introduction, IMRT has quickly emerged as the radiation modality of choice for rNPC as well, with or without the use of chemotherapy. Its efficacy has been established in various studies, with documented long-term OS rates ranging from 45% to 65%.[48-56] Yet, most of the patients in those studies were treated with conventional 2D-RT in the pre-IMRT era. In a recent study conducted by Kong et al,[56] 77 patients received salvage IMRT for rNPC after a definitive course of primary IMRT. While the median OS and PFS were 37.0 and 20.5 months, respectively, of particular note is the re-irradiation toxicity. Of 34 patients, 18 died from treatment-induced severe adverse effects without evidence of disease progression during the study, including mucosal necrosis, temporal lobe necrosis, and cranial neuropathy,[56] reflecting the limitations of salvage IMRT in the modern IMRT era. Other radiation modalities have been proposed, including particle therapy using proton and carbon ions,[57] but long-term data are not yet available.

Chemotherapy

Chemotherapy is another important modality in managing NPC, and it is often combined with RT in the intermediate and advanced stages of NPC. The benefit of CRT was well-illustrated in a meta-analysis of seven trials, which showed significantly improved OS and 10-year PFS in the CRT group compared with the RT-alone group.[58] A platinum-based regimen is often used as the chemotherapy of choice, in which cisplatin is most commonly used.[10]

While it is clear that chemotherapy is essential in the treatment of advanced NPC, its value as an add-on induction therapy (preceding CRT) and adjuvant therapy (following CRT) is less clear. Regarding induction therapy, a phase III trial recently showed that the addition of docetaxel, cisplatin, and fluorouracil prior to CRT was superior to CRT alone in terms of OS and PFS at 3 years,[59] although another trial using cisplatin and fluorouracil as induction therapy failed to show significant differences in OS.[60] The role of induction therapy requires further confirmation from other ongoing phase III trials.

Meanwhile, the use of adjuvant chemotherapy following CRT is debatable. A phase III trial with a median follow-up of 68.4 months failed to show significantly improved OS and PFS after adding cisplatin and fluorouracil as adjuvant therapy post-CRT in locally advanced NPC,[61] but another study suggested adjuvant chemotherapy might be reserved for high-risk patients defined by post-treatment residual EBV DNA.[62,63] It should be noted, however, that the benefit of more intensive therapy may be limited by the late toxicities of high cumulative doses of chemotherapy, most notably cisplatin, which are not reported in some of the studies.[60,64]

Platinum-containing doublet regimens remain the first-line systemic treatment for recurrent or metastatic NPC. Cisplatin and fluorouracil have been the conventional choices.[10] A recent study by Zhang et al[65] demonstrated that the combination of cisplatin plus gemcitabine was superior to the combination of cisplatin and fluorouracil, in terms of median PFS (7.0 vs 5.6 months; hazard ratio=0.55; 95% confidence interval, 0.44-0.68), although the cisplatin-gemcitabine group experienced more haematological toxicity, such as grade-3 or higher leukopenia, neutropenia, and thrombocytopenia.[65] This randomised controlled trial has thus established the role of cisplatin and gemcitabine combination as the chemotherapy of choice in recurrent or metastatic NPC.

Surgery and targeted therapy

As mentioned above, surgery is usually not considered in the routine management of NPC; yet salvage therapy can be considered an option for selected patients with local recurrence in the neck.[66] Molecular targeted therapy is considered hopeful

for many other types of carcinoma, but its efficacy in treating NPC has been disappointing; studies of inhibitors of epidermal growth factor receptor (eg cetuximab) and vascular endothelial growth factor (eg sunitinib) failed to show superiority over standard treatments, and were largely limited to phase II trials.[8] Lee et al[8] attributed its failure to the scarcity of authentic NPC models that can be utilised in the preclinical studies of new drugs, and increased incidence of drug-related toxicities such as bleeding. The development of immunotherapy is therefore exciting as it presents a new hope for managing NPC.

Immunotherapy

The presence of EBV and the expression of viral antigens in almost all NPC cases make this disease an attractive target for the development of immunotherapy. For example, EBV nuclear antigen I (EBNA1) and latent membrane protein 2 (LMP2) are frequently expressed in EBV-associated NPC, and a recombinant virus–based vaccine that encodes an inactive fusion protein containing fragments of EBNA1 and LMP2 was shown to be effective in inducing T-cell response in a local phase I trial.[67] The vaccine is currently being tested in a phase II clinical trial (NCT01094405).

As EBV that persists as a latent infection is controlled by cytotoxic T lymphocytes (CTL),[68] it follows that the use of EBV-specific CTL for NPC appears logical as a treatment strategy. Adoptive immunotherapy that includes infusion of autologous CTL has been tested in a number of clinical trials, and the results have been promising. For example, a study in Singapore showed that chemotherapy followed by EBV-specific CTL achieved a response rate (full or partial) of 71.4% in 38 patients,[69] and a phase III trial is currently underway to assess its efficacy (NCT02578641).

Among all the immunotherapies available, checkpoint inhibitors seem to be the most rapidly developing. Programmed death ligand–1 (PD-L1) was found to be expressed on antigen-presenting cells, and its interaction with the programmed death–1 (PD-1) receptor on T cells inhibits downstream signalling of T cell receptors.[70] Tumour-associated PD-L1 was also found to mediate immune suppression by various other mechanisms, such as facilitating T cell apoptosis and inducing regulatory T cells.[71] With PD-L1 expressed in many different carcinomas,[72] blockade of PD-L1 and/or the PD-1 receptor has become the focus of new cancer drug development in the past 5 years.

While PD-L1 inhibitor has recently gained much attention in the treatment of non–small-cell lung cancer,[73] its progress in the treatment of advanced NPC is exciting and much awaited. Pembrolizumab was shown to be well-tolerated with significant anti-tumour activity in NPC in a phase Ib trial,[74] and is currently in a phase II trial to confirm the response rate and efficacy in terms of improvement in OS (NCT02611960). Nivolumab has just completed phase II trials; the preliminary results showed that it is active in heavily pre-treated recurrent or metastatic patients,[75,76] and that PD-L1 expression may predict benefits from nivolumab.[75]

Conclusion

Once a nightmare in the eyes of many Hong Kong inhabitants, NPC has become less prevalent in southern China, but it still poses a threat to Hong Kong citizens as it was ranked as the 10th most common cancer in the city.[3] With clearer understanding of its pathophysiology and advances in technology, it is expected that more refined treatment strategies and novel therapeutic agents will be available in the near future.

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