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Conference Report

International collaborations preparing for a cancer "moon shot": a summary of the Sino-US Symposium on Head and Neck Cancer

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The earliest written record about cancer dates back to approximately 3000 BC [1] and, despite tremendous developments in medicine, the mainstream opinion towards cancer remains that "there is no treatment". It must be admitted that most cancers are still far from being preventable and curable diseases, especially cancers such as those of the head and neck, which are prevalent in developing countries[2].

Head and neck cancers account for 3% of adult malignancies in the United States, with 52 000 new cases and 11 500 deaths forecast for 2012[2]. The incidence is much higher in some Asian countries than in western countries. For example, the age-standardized incidence of oral cavity cancer is 18/100 000 in Karachi, South Pakistan and 5/100 000 in India[3]. In China, nasopharyngeal carcinoma (NPC) is the 11th most common malignancy, with an incidence of 27.2/100 000 for men and 11.3/100 000 for women in the highest incidence area[4].

Oncologists and scientists in the field of head and neck cancer exchanged their research findings and clinical experiences in the Sino-USA Symposium on Head and Neck Cancer, which was held January 6–7, 2012 in Guangzhou, China. The symposium was jointly organized by Sun Yat-sen University Cancer Center (SYSUCC) and the University of Texas MD Anderson Cancer Center (MDACC). The Guangdong Provincial Anti-Cancer Association and the *Chinese Journal of Cancer* also helped in organizing the conference. Speakers were from China (SYSUCC, the Chinese University of Hong Kong, Tianjin Medical University Cancer Institute and Hospital, and Fudan University Shanghai Cancer Center) and the United States (MDACC). The presentations covered most kinds of head and neck cancers and included both basic and clinical research progress. In particular, NPC was discussed in depth. The symposium explored the reality that cancer is complex and numerous questions remain to be answered, even though there has already been an enormous effort into research. International exchanges of experience and in-depth cooperation are definitely needed to improve our capability of caring for cancer patients. In this article, we provide highlights of the presentations.

Cancer's Moon Shot Based on Cutting-Edge Technologies

In President John F. Kennedy's speech at Rice University in 1962 about the U.S. space effort, he said, "We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energy and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win ..."[5] In the opening of the conference, Prof. Ronald A. DePinho, the new president of MDACC, titled his keynote speech "Cancer's Moon Shot".

On our way to making cancer history, where are we now? Prof. DePinho said that nearly half of all individuals would develop cancer in their lifetime. Yet success rates of anti-cancer drug development have remained disappointing through the years, and many barriers still exist that inhibit the progress, including limited insights into the factors driving cancer genesis, only elementary knowledge of the cancer genome, a poor understanding of the target's "biology", lack of insight into appropriate combination therapies, and a challenged cancer drug development system. Cancer is a complex disease, with highly interconnected, redundant, and dynamic signaling networks that allow a tumor to bypass a single-point intervention. Co-extinction is the only way patients may escape the misfortune of tumor recurrence or metastasis.

Thus, we are facing a thorny problem threatening many lives, and it seems that the difficulties of curing cancer are out of our grasp. Yet there is still hope. Enormous progress has been made in genome technology, producing much higher efficiency at much lower cost, and this technology will offer us a huge

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amount of data on cancer genes. The Cancer Genome Atlas Project, initiated in 2005, is generating valuable information about cancer-associated genetic changes [6]. Transformative technologies—including RNA interference, ORFeome, gene delivery and nanotechnology, in silico biology & chemistry, quantitative analysis of biospecimens, and molecular imaging—are available and widely used for cancer research.

Although many assays, systems, and models are being used to assess gene functions, it seems hard to capture all hallmark features of cancers. We still have to elucidate the internal and external mechanisms driving the genesis of cancer to enable prevention and early detection. The molecular characteristics of cancer need to be determined, which will provide prognostic information and guide individualized treatment. Academic labs, industry, and clinical partners must be all involved in validating candidate targets and effective treatments, supported by grants, corporate funding, and philanthrophy. Multidisciplinary think tanks, scientific and business plans, implementation, execution, and monitoring will be the succeeding steps.

Prof. DePinho also announced some inspiring news: he and scientists working with him have set an ambitious goal to cure five varieties of cancer, something "akin to a moon shot" as he expressed it. The International Cancer Genome Consortium, involving 39 projects in four continents, is using high-throughput DNA sequencing to examine 50 types of tumor, as one of the early steps toward this great goal. Causative and incidental mutations in cancers should be revealed. In addition, Prof. DePinho's broad experiences in clinical service, basic research, and related endeavors provide an advantage in forming a bridge from research to clinical treatment. The state of Texas is creating a $3 billion cancer-research fund to help to pay for this project, and local philanthropists are also contributing[7].

NPC as A Model for Cancer Research

Genomic instability, virus infection, and environmental factors are all major etiologies of cancers. In NPC genesis, all three are involved, meaning that NPC should be a good model for cancer research. Indeed, Prof. Yi-Xin Zeng, the President of SYSUCC, used "Nasopharyngeal Carcinoma: a Model for Cancer Research" as the title of his talk at the conference. He discussed the hypothesis of double selection for NPC development that was introduced by Dolly Huang in 2004. Based on the Knudson two-hit hypothesis of tumorigenesis [8], that hypothesis for NPC development incorporated genetic background, EBV infection, and environmental carcinogens into the multiple steps of tumorigenesis. Viral infection as a cause of NPC may be amenable to attack. Hepatitis B virus (HBV) vaccine was successfully developed for the prevention of HBV infection and has helped decrease the incidence of hepatocellular carcinoma. Vaccines for human papilloma virus (HPV) and *helicobacter pylori* (HP) are now in clinical trials against cervical cancer and stomach cancer, respectively. A vaccine against NPC would definitely be welcomed, but our limited knowledge about the role of EBV in the genesis of NPC is an obstacle.

It has been realized for decades that cancer is a genetic disease. Germline variations in an NPC population were explored using a genome-wide association study (GWAS) by Prof. Zeng's group, who reported their results in 2010 in *Nature Genetics*[9]. Their study identified three new susceptibility loci, and they confirmed the role of human leukocyte antigen (HLA) by revealing independent associations at the three loci. Prof. Zeng said that the outcomes desired from GWAS were an understanding of pathogenesis, disease risk prediction, first-level prevention, and early detection.

Somatic gene variations were also investigated by Prof Zeng's group. Detecting tumor samples from 150 patients with NPC, only 2 carried the same mutation in *AKAP4*, suggesting countless individualized mutation profiles. A wide variety of somatic gene variations may hinder us from easily finding the most important loci contributing to NPC genesis. Another possibility is that there is no set of a few important loci; cancer might indeed have limitless kinds of genomic instability. This group further demonstrated that increasing genomic instability could induce stem-like cancer cells and that chemical treatments aiding genomic stability could enhance the antitumor effects of chemotherapeutics.

Advances in Head and Neck Cancer Management

Etiology and prognosis of head and neck cancer

HPV has recently been proven to be etiologically associated with 20%–25% of squamous cell carcinomas of the head and neck (SCCHN), especially in oropharyngeal cancer, as Prof. Scott M. Lippman of MDACC presented. HPV-positive SCCHN represents a distinct clinical entity with favorable prognosis compared with HPV-negative patients, and the incidence of HPV-positive SCCHN is increasing in developed countries. Prof. Lippman said this new entity needs more investigation in terms of its genesis and clinical behavior.

Genetic techniques have enabled scientists to find more information in the cancer patient's genome. Prof. Jeffrey N. Myers of MDACC and his colleagues have conducted a comprehensive investigation of oral squamous cell carcinoma, and they found that in addition to mutations in *TP53* and *p16*, mutations in the genes for Notch, PI-3 kinase, H-Ras, caspase-8, and FBXW-7 are common. In his presentation, Prof. Myers summarized

their potential significance in the genesis and progression of oral cancer and gave insight as to how these findings might be used to help patients with oral squamous cell carcinoma.

The clinical epidemiologic trends of thyroid carcinoma

According to Prof. Ming Gao of the Tianjin Medical University Cancer Institute and Hospital, the epidemiology of thyroid carcinoma has been changing. The incidence of thyroid carcinoma increased 3–4 times from the 1970s to 2010, both in the United States and in the Tianjin district of China. The pathologic composition of thyroid carcinoma also changed significantly, with the percentage of papillary thyroid carcinoma (PTC) increasing from around 70% in the 1960s to above 95% in 2010, and the percentages of follicular thyroid carcinoma, medullar thyroid carcinoma, and anaplastic thyroid carcinoma all decreasing. Studies comparing familial and sporadic PTC revealed that patients with familial PTC were younger, had more multifocal or bilateral-focal disease, and tended to have more cervical lymph node metastasis. When comparing clinical characteristics between males and females, the average age of onset in females tended to be earlier, female patients' disease was prone to combine with Hashimoto's thyroiditis, and male patients were prone to have tumors of higher malignancy.

The proportion of bilateral lesions in PTC patients has increased from about 10% in the 1990s to nearly 30% in 2010, and the proportion of PTC combined with Hashimoto's thyroiditis increased from 2% to nearly 10% during that period. Due to improved diagnostic techniques and public awareness of health care, more patients have been diagnosed to have papillary thyroid microcarcinoma (PTMC), which made up nearly 40% of PTC at the Tianjin Medical University Cancer Institute and Hospital in 2010. Of the patients with clinical N0 PTMC, 23.1% have pathologically confirmed N1 disease. Finally, the prevalence of thyroid carcinoma is much higher in high-iodine areas than in normal-iodine areas. All these characteristics will help oncologists define a standardized therapy, suggest personalized treatment, and develop a prevention strategy against thyroid carcinoma.

Treatment of head and neck cancer

Prof. Randal S. Weber of MDACC spoke on evidence-based surgical management of oral tongue cancer. He emphasized adequate tumor staging, neck dissection for tumors of 4 mm or greater in thickness or depth of invasion, and considerations about post-operative radiation for adverse pathologic features.

Surgery is still the mainstay for head and neck cancer management. Prof. Zhu-Ming Guo of SYSUCC elaborated the principles of surgery for different stages of thyroid carcinoma and discussed the controversy concerning surgery extension, including primary tumor resection and neck dissection. He also showed that using harmonic equipment in the surgery for thyroid carcinoma provided better hemostasis and shortened surgical time and incision length relative to traditional surgical equipment. The role of non-surgical treatment in advanced thyroid carcinoma—especially targeted therapy such as sorafenib, the small-molecule inhibitor of several tyrosine protein kinases—was discussed by Prof. Ming Gao.

Two surgical oncologists from SYSUCC shared their experience in reconstructive surgery for head and neck cancer patients. Dr. Wei-Wei Liu introduced the application of anterolateral thigh flaps in the reconstruction of head and neck defects, and Dr. Xue-Kui Liu talked about the value of titanium mesh in laryngeal framework reconstruction for glottis cancer patients after frontolateral vertical partial laryngectomy.

Chemotherapy is widely used for head and neck cancer. Prof. Lun Zhang of the Tianjin Medical University Cancer Institute and Hospital has found that STAT3 can influence SCCHN sensitivity to chemotherapy via regulating miR-21 transcription, which may help to predict a tumor's reaction to chemotherapy.

Targeted therapy is becoming a critical part of antitumor treatment. The role of targeted agents as induction therapy in SCCHN was reviewed by Dr. Ye Guo of Fudan University Shanghai Center. Given that adding cetuximab, an anti–epithelial growth factor receptor monoclonal antibody, to concurrent chemoradiotherapy did not improve the survival of head and neck cancer patients, they started a phase Ⅱ trial to investigate the role of targeted therapy in an induction model. After two cycles of PF regimen plus nimotuzumab, 15.4% of the patients who underwent surgery as local treatment achieved complete pathologic response; the long-term survival data are awaited.

In summary, multimodality treatments are of great importance for curing, function preservation, and defect reconstruction of head and neck cancer patients and oncologists are trying to improve the treatment outcome in all possible ways.

Breakthroughs in NPC Research

Genesis and metastasis of NPC

Epstin-Barr virus (EBV) is best known to be associated with certain forms of cancer, particularly Hodgkin's lymphoma, Burkitt's lymphoma, and NPC. The complement receptor type 2 (CR2) has been known as the receptor for EBV infection of B lymphocytes for

long time, but the mechanism of EBV infection of epithelial cells is not fully understood. Prof. Mu-Sheng Zeng of SYSUCC presented the novel findings of his group: a receptor named gHgLR was identified as an essential part of the entry receptor of EBV into epithelial cells. This discovery may help us to understand the genesis of NPC and to look for new targets for antiviral drug development.

The distinctive ethnic and geographic distributions of NPC suggest that both environmental factors and genetic traits may contribute to its genesis. Results from Prof. Wei-Hua Jia's group suggest that consumption of Canton-style salted fish and other preserved foods during childhood is an independent risk factor for NPC, whereas Canton-style herbal tea, herbal slow-cooked soup, and tea consumption have protective effects against NPC. As for genetic predisposition, two SNPs located in DNA repair genes and polymorphisms of both *CYP2E1* and *TLR3* were all related to NPC risk. A contribution from gene-environment interactions to the genesis of NPC was also found in their research[10].

Prof. Kwok-Wai Lo of the Chinese University of Hong Kong has previously shown that inactivation of the tumor suppressor gene *RASSF1A* is related to the development of NPC[11]. During this conference, he introduced new findings: RASSF1A is a vital factor that ensures the sequential progression of mitosis by regulating the activity of APCcdc20 through its D-box motifs, and the first two D-boxes are unique to RASSF1A among RASSF1 family members[12]. Inactivation of RASSF1A may contribute to the genesis of NPC by disabling mitosis progression.

Metastasis is regarded as a late stage of cancer development, and patients with metastasis have poor prognosis. After genomic expression profiling, as well as *in vitro* and *in vivo* experiments, Prof. Chao-Nan Qian has found that glycosylated serglycin promotes NPC metastasis via autocrine and paracrine routes[13]. This novel finding might shed light on the metastasis research in other malignancies in which seglycin is also highly expressed[14].

NPC classification and prognostic indicators

Since the first NPC patient was reported in 1837 by the French physician Derand-Fardel, the histological classification of NPC has gone through several versions. However, the current WHO histological classification of NPC does not reflect its morphologic heterogeneity and is insufficient for prognosis prediction of NPC patients, according to Prof. Jian-Yong Shao of SYSUCC. Therefore, a multicenter study was initiated by Prof. Shao, aiming to create a new classification system. At the conference, he reported that, based on a study on 3839 cases, NPC could be grouped into undifferentiated epithelial cell carcinoma (UECC), undifferentiated spindle cell carcinoma (USCC), mixed undifferentiated epithelial-spindle cell carcinoma (UESCC), and squamous cell carcinoma (SCC). This classification is significantly related to patient survival, with a 5-year disease-specific survival of 76.4% for UECC, 66.0% for UESCC, 56.0% for USCC, and 32.7% for SCC.

Prof. Shao has also succeeded in using a support vector machine (SVM)–based method to develop a prognostic classifier that included patient demographic information and the expression levels of seven proteins: Epstein-Barr virus latency membrane protein-1, CD147, caveolin-1, phopho-P70S6 kniase, matrix metallo-proteinase 11, survivin, and secreted protein acidic and rich in cysteine (SPARC). Other work on prognostic markers comes from Prof. Qian's group[13], who found glycosylated serglycin and its downstream molecules to be independent prognostic factors of NPC as well as metastasis promoters.

Multimodality treatment for NPC

Radiotherapy is the first choice for treating non-metastatic NPC patients, and chemotherapy provides further survival benefits for patients with advanced disease. However, the combination of radiotherapy and chemotherapy is being studied for both early-stage and late-stage NPC patients. The results of two randomized phase Ⅲ clinical trials from SYSUCC were reported at the conference. Prof. Hai-Qiang Mai showed the audience 5-year survival results from 230 patients with stage II NPC who underwent conventional radiotherapy with or without concurrent cisplatin treatment [15]. Concurrent chemotherapy significantly prolonged the overall survival, progression-free survival, and distant metastasis-free survival of stage II NPC patients. Prof. Mai also said that the value of concurrent chemotherapy should be re-evaluated in the era of intensity-modulated radiotherapy.

Today, concurrent chemoradiotherapy is the standard regimen for locoregionally advanced NPC patients. Whether neo-adjuvant or adjuvant chemotherapy can decrease the rate of treatment failure for those patients is still inconclusive. Prof. Jun Ma reported the preliminary results of a multicenter randomized controlled phase Ⅲ trial comparing concurrent chemoradiotherapy with or without adjuvant chemotherapy [16]. They recruited 508 patients with non-metastatic stage III–IV disease, and did not find significant differences between the two groups in terms of failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival. Thus, the addition of three cycles of adjuvant cisplatin and 5-fluorouracil chemotherapy to concurrent chemo-radiotherapy did not improve the survival of patients with locoregionally advanced NPC.

The value of targeted therapy for patients with metastatic NPC is under investigation. Prof. Li Zhang introduced preclinical studies and clinical trials undertaken at SYSUCC. The AKT inhibitor MK-2206 inhibited the viability of NPC cell lines *in vitro* and remarkably decreased xenograft tumor size *in vivo*. The VEGF inhibitors sorafenib and VEGF-trap were used to treat late-stage NPC patients in a phase Ⅱ and phase Ⅰ trials, respectively, and the early responses of patients were quite promising. The antitumor efficacy of the c-Kit inhibitor famitinib was also investigated in an ongoing phase Ⅱ clinical trial at SYSUCC. These medicines may shed light on the treatment for locoregionally recurrent and metastatic NPC.

Prospective

The human's dream of a "moon shot" came true when astronauts Neil Armstrong and Edwin (Buzz) Aldrin landed on the moon on July 20, 1969, walked on its surface, and safely returned to the earth on July 24. That dream took only 9 years to realize, which is so brief compared to the extended history of our fight against cancer. Finding way to wipe out cancer and in doing so to write cancer history is absolutely a herculean task, but given the prevalence of cancer worldwide, it is an urgent goal. We are fortunate to be aided by the rapid developments in molecular biology and related scientific fields, which are accelerating our studies of multiple approaches to preventing and curing cancer. However, we should keep in mind that the complexity of the microworld is not less than that of outer space. Moreover, conquering cancer cannot be achieved only through the endeavors of researchers and oncologists. Our entire society should join in this effort using multiple approaches, including public education, research facility development, research resource expansion, population-based cancer prevention and early detection, neuropsychologic intervention, advanced medical equipment and facilities, evidence-based clinical management, personalized medicine, medical information collection and analysis, and others. We would like to provide our future generations with the gift of a life without the fear of cancer.

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