Critical Issues in Head and Neck Oncology

Key Concepts from the Sixth THNO Meeting

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Preface

The sixth Trends in Head and Neck Oncology (THNO-6) took place in the Meridien Hotel in Nice, France, November 2–4, 2017, and was organized by the same coordinating team as the fifth version with support of Pharma and practical logistical support of Congress Care. This time, the conference was endorsed by the European Head and Neck Society (EHNS) and the European Organization for Research and Treatment of Cancer (EORTC). As on previous occasions, the setup was educational, with a multidisciplinary focus. Case presentations, organized by colleagues from the Centre Antoine Lacassagne in Nice and some members of the coordinating team, induced a lively interaction between faculty and audience and underlined the importance of individualized patient care. Thanks to the dedication of all faculty members this book will be available within a year following the actual meeting, guaranteeing the most up-to-date information in this rapidly evolving field. We are most grateful to all faculty members for their efforts in realizing this important goal.

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Johannes Berkhof

Introduction

Human papillomavirus (HPV) is the main cause of cervical cancer and also causes a substantial number of cancers at other sites. It was recently estimated that approximately 29,000 oropharyngeal cancers and 8000 oral cavity and larynx cancers, occurring globally in year 2012, could be attributed to HPV and that about 80% of HPV-related head and neck cancer cases occurred in men [1]. Besides, an upward surge in HPV-associated oropharyngeal cancer has been observed in the United States (US) and some European countries in the last years, in particular in males [2–5]. US projections indicate that in 2020, oropharyngeal cancer will occur more frequently than cervical cancer [2]. The disproportionate burden and rising incidence of HPV-associated head and neck cancers in men has ignited discussion on the vaccination of boys. So far, most countries with a publicly funded HPV vaccination programme have targeted girls only since the main focus is on prevention of cervical cancer. The HPV-related burden in men is nowadays being recognized but a long-standing debate exists on whether there is sufficient evidence on the effects of the vaccine against cancer in men and whether the effects are large enough to justify the extra costs of vaccinating boys. In the following, I give an overview of the current evidence on the efficacy and expected impact of HPV vaccination in men and women with a focus on oropharyngeal cancer.

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HPV Vaccines

There are three HPV vaccines on the market registered for use from the age of 9 years. The vaccines are licensed for the prevention of lesions in the cervix, vulva, vagina, and anus, but not for the prevention of head and neck cancers. Cervarix® (GSK) is a bivalent vaccine that protects against HPV16 and HPV18 infections and also provides some cross-protection against a few other oncogenic HPV types [6–8]. Cervarix is registered for females and males in Europe and only for females in the US. Gardasil® (Merck & Co) is a quadrivalent vaccine that protects against HPV16 and HPV18 and also protects against HPV6 and HPV11, responsible for most cases of genital warts and recurrent respiratory papillomatosis. Gardasil is registered for females and males in both Europe and the US. Since 2016, a nonavalent vaccine Gardasil9® (Merck & Co) has become available with the main purpose to offer improved protection against cervical cancer and high-grade cervical dysplasia. For head and neck cancer prevention, the additional benefit of a nonavalent vaccine as compared to a bivalent or quadrivalent vaccine is limited as HPV16 accounts for about 80% of the HPV DNA positive cases and for about 90% of HPV DNA positive oropharyngeal cancers [9].

Early End-Points

The main reason that the current HPV vaccines are not licensed for the prevention of head and neck cancers is that clinical trials were only able to show an effect against cervical and other anogenital premalignant lesions [10–14]. Unlike anogenital cancers, HPV-positive head and neck cancers have no clearly visible premalignant end-point thus their histopathological progression remains poorly defined [15]. Moreover, the mean age of HPV-positive oropharyngeal cancer is above 50 years [16] and this means that if regulatory bodies demand a significant effect on cancer incidences from trials targeting adolescents and young adults, vaccine licensure against oropharyngeal cancer will be postponed for another three to four decades.

The only alternative to showing an effect on dysplasia is to measure oral HPV infections. However, establishing a link from oral HPV infection to cancer and precancer is hard, if not impossible. Studies will never be large enough to show an association between oral infection and invasive cancer. Furthermore, establishing a link between oral infection and subclinical dysplasia in healthy subjects seems ethically unfeasible. Nevertheless, case-control studies have provided strong support that HPV exposure is necessary for HPV-positive oropharyngeal cancer [16, 17] and it is widely accepted that HPV-positive head and neck cancers cannot develop without a preceding HPV infection.

The effect of HPV vaccination on the occurrence of oral infections has recently been studied in two populations. Participants in those studies were asked to collect rinse and gargle samples using a mouthwash. The first population consisted of women participating in a randomized trial with the bivalent vaccine [18]. The use of

randomization has the advantage that it minimizes bias related to demographic differences between the vaccine and the control arm. The effect of vaccination on oral vaccine-type HPV infections was estimated at 93% (1/2910 in vaccinated women versus 15/2924 in unvaccinated women). The second population was the National Health and Nutrition Examination Survey (NHANES), a representative subset of the US population. Two cross-sectional analyses on NHANES indicated that the occurrence of oral quadrivalent vaccine-type HPV infections was about 90% lower in vaccinated as compared to unvaccinated men and women [19, 20]. Limitations of the NHANES population are that vaccine status is self-reported and that subjects are not randomized with respect to vaccination. Regarding the latter, vaccine-associated effects were robust against confounders such as age, sex, sexual behaviour, smoking, and race [20]. The decision to get vaccinated may have been influenced by factors that were not measured, but it is unlikely that only unobserved confounders were responsible for the strong association between vaccination and oral infections. In another recent study, HPV16 and HPV18 specific antibodies in the oral mucosa of adult males were induced by vaccination, but the study was not able to demonstrate whether the antibody levels were sufficient to offer protection against incident infections [21]. To conclude, the current evidence on the effect of vaccines on infections and vaccine-induced antibodies in the oral region seems sufficient to include oropharyngeal cancer in the impact and cost-effectiveness assessments of vaccination strategies, but for vaccine licensure there is a need for more data on the effect of vaccination on infections and antibodies in the oral region.

Herd Effects

Most HPV vaccination programmes target girls because women experience the greatest HPV-related disease burden. Of all 630,000 new HPV-related cancers worldwide in 2016, 570,000 cases occurred in women [1]. Nevertheless, exclusion of boys from the programme has raised equity concerns because HPV-related cancers occur in, both, women and men. A widely used argument against sex-neutral vaccination is that vaccination of girls confers indirect protective effects or herd effects to men. This means that heterosexual men would be protected against HPV-associated diseases if the coverage of the girls' only vaccination programme is high. The required coverage level of a girls' only programme is, however, difficult to assess because herd effects depend on sexual network features and natural immunity after viral clearance [22].

For estimating herd effects, we usually rely on mathematical HPV infection models that describe the transmission of HPV in sexual networks. HPV infection models require many assumptions and can have a different architecture leading to uncertain and potentially inconsistent results. To study whether predictions provided by independent models were consistent, in a recent study, sixteen independent modelling teams provided estimates of the reduction in HPV16 and HPV18 under different vaccine coverage scenarios [23]. The results from the modelling teams were strikingly consistent despite the fact that models were developed in different

settings and calibrated to different data. A main result was that at 80% coverage of a girls' only programme, the HPV16 prevalence would decrease by 93% in women and by 83% in men. If both girls and boys were vaccinated with a coverage of 80%, HPV16 would virtually be eliminated from the population in most models. At a coverage of 60% among girls and boys, HPV16 would be reduced by 90%. Since the majority of immunization programmes shows coverage levels between 50 and 80%, sex-neutral vaccination is expected to reduce HPV16 and HPV18 prevalence to a very low level. Two important limitations of the models are that they only consider heterosexual networks and do not take differences in site-specific transmission into account. Those limitations are not likely to change the general message: sex-neutral vaccination can be important for reducing the prevalence of HPV to a very low level when a girls' only programme fails to achieve a coverage similar to those observed for paediatric vaccines.

A number of studies have emerged that aim to measure herd effects in real life data. In an Australian study on men attending a sexual clinic after a positive test for *Chlamydia trachomatis* [24], a significant reduction in the prevalence of the HPV types targeted by the quadrivalent vaccine from 18 to 7% was observed in Australian-born men before and after the start of the vaccination programme. In the last three calendar years of the study (2013–2015), the prevalence of the HPV types targeted by the vaccine was only 3%. As expected, no decrease in prevalence was observed for the HPV types that were not targeted by the vaccine. Another interesting study is a Finnish randomized trial where communities were either randomized to girls' only or sex-neutral vaccination with the bivalent vaccine [25]. A herd effect for HPV18 in cervical samples was observed in both study arms. A herd effect was not observed for HPV16 which may be related to the low vaccine coverage of 20% among boys and 45% among girls attending junior high school. The larger herd effect for HPV18 as compared to HPV16 in the Finnish trial concurs with intuition because HPV16 has a higher basic reproductive number than other HPV types [26, 27]. This means that a subject infected with HPV16 infects on average a larger number of susceptible subjects than a subject infected with another HPV type and hence it becomes more difficult to eliminate HPV16 from the population.

In a few years, it will be possible to measure herd effects in nationwide cervical cancer screening registries provided they are linked to vaccination registries. This information will be very important when developing cervical cancer screening algorithms for vaccinated cohorts, but its value for head and neck cancer prevention will be limited because herd effects observed in cervical cancer screening are expected to be different from herd effects in future head and neck cancers. The difference will be most pronounced in countries with a girls' only vaccination programme. Then, herd effects in unvaccinated women will be second-order indirect effects occurring because men have a lower probability of infecting unvaccinated women since they themselves will be indirectly protected by the girls' only vaccination programme. Therefore, mathematical models will still be needed to estimate the reduction of HPV infections in men and to facilitate decision-making on sex-neutral vaccination.

The Effect of Vaccinating Boys on Cancer in Men

Although herd effects are important to reduce HPV infections in the general population, the question remains whether vaccination of men would contribute sufficiently to the prevention of cancer in men to justify a sex-neutral vaccination programme. In a Dutch evidence synthesis study conducted in 2015 [28], the effect of vaccinating boys on future cancers in men was calculated. The cancers considered were cancers of the penis, anus, and anal canal, and squamous cell carcinomas of the oropharynx, including the base of tongue and tonsils (international classification of diseases 10th revision code C60, C21, and C01, C09 and C10). HPV aetiological fractions for the different tumour sites were obtained from several sources [29–31] and elevated cancer risks in homosexual and bisexual men (men having sex with men; MSM) as compared to heterosexual men were taken into account [32]. HPV-associated oral cavity and larynx carcinoma were not considered in this study because their burden is low relative to that of HPV-related oropharynx cancer [1]. The herd effects in men achieved when vaccinating girls only were estimated by a mathematical HPV transmission model [33]. The transmission model predicted that a 10% reduction of HPV16 or HPV18 among women would induce an 8% reduction of HPV16 or HPV18 among men. After taking these herd effects into account, the conclusion of the evidence synthesis study [28] was that vaccination of boys would still confer a substantial reduction in future cancer in men. At 60% vaccine coverage among girls, about 800 boys would need to be vaccinated to prevent an additional future cancer in men. Tumour site specific numbers were about 2000 boys for oropharyngeal cancer and anal cancer and 3500 for penile cancer. When the coverage in girls was increased to 90%, tumour-specific numbers were about 6500 boys for oropharyngeal cancer, 2600 for anal cancer, and nearly 30,000 for penile cancer. In the latter situation, the majority of the cancers prevented by vaccinating boys were anal cancers, which underscores the relevance of HPV vaccination for cancer prevention in MSM.

In a country with a girls' only vaccination programme and a coverage of 90%, sex-neutral vaccination can still be motivated as a strategy to prevent cancer in MSM, but targeted vaccination of adolescent and adult MSM has also been suggested. Targeted MSM vaccination is less costly than sex-neutral vaccination, but it is not effective in the subset of the HPV-positive MSM. Considering that HPV infections occur soon after the initiation of sexual debut, concerns can be raised with respect to the effectiveness of strategies for early identification of sexually naïve MSMs. Nonetheless, a modelling study indicated that targeted MSM vaccination may be cost-effective up to the age of 40 [34]. It is also important to understand that targeted MSM vaccination does not preclude sex-neutral vaccination and vice versa. After implementation of sex-neutral vaccination, targeted MSM vaccination may still be used as a catch-up for older age groups and as an option for MSM who spent their childhood in a different country.

Vaccination Coverage and Programme Resilience

Several modellers have pointed out that even when the coverage of a girls' only vaccination programme is low, it is more efficient to increase the uptake among girls than to vaccinate boys in order to reduce the HPV prevalence in the general population [35, 36]. This argument supports prioritization of efforts to increase the uptake among girls, but it is uncertain whether such efforts would be successful. So far, HPV vaccination programmes in most countries have achieved a coverage far below the 90% target level for paediatric vaccines. A main reason for the limited coverage among girls is that there are recurring concerns about vaccine safety and side effects [37, 38]. An alarming example is the HPV vaccination programme in Denmark where the vaccine coverage decreased from about 80 to 20% in 2015 as a result of an alleged association between HPV vaccine and Postural Orthostatic Tachycardia Syndrome (POTS) [39]. To assess whether these concerns are supported by data, the European Medicines Agency (EMA; www.ema.europa.eu) conducted a large study on the incidence of POTS and Complex Regional Pain Syndrome (CRPS). The EMA compared approximately 60,000 women vaccinated with Gardasil and 40,000 women vaccinated with Cervarix with placebo cohorts but did not find a significant association between adverse events and vaccination status. Besides, the POTS cases in Denmark were mainly observed in one centre suggesting considerable heterogeneity in the diagnosis of POTS.

The results from the EMA are reassuring, but the Danish example clearly indicates that HPV vaccination programmes are vulnerable. The sudden sharp decline in vaccine coverage that has happened in Denmark may happen in any other country as well. Sex-neutral vaccination has been suggested to make programmes more resilient against temporary changes in the vaccination coverage. A recent modelling study predicted that if the vaccine coverage was halved for a period of 5 years, then a sex-neutral vaccination would be about 12-fold more resilient than girls' only vaccination in terms of the percentage reduction in HPV prevalence in the female population [40]. Therefore, as long as HPV vaccine coverage is unpredictable, sex-neutral vaccination may be implemented to stabilize the impact of the programme against temporary variations in coverage.

Economic Considerations

So far, cost-effectiveness studies on sex-neutral vaccination have not yielded consistent results. Although some studies were positive, most studies recommended against sex-neutral vaccination [41]. An explanation for this finding is that some economic studies did not consider all non-cervical health outcomes in their main analysis. In a recent review, it was calculated that the standard measure in cost-effectiveness studies, that is the incremental cost-effectiveness ratio, would decrease 3.9-fold if all non-cervical disease had been taken into account, including oropharyngeal cancer and genital warts, as compared to cervical cancer only [41]. Of

course, negative results in cost-effectiveness studies are also strongly driven by the HPV transmission dynamics. A Canadian study illustrated that when herd effects from a girls' only programme are ignored, vaccination of boys is cost-effective even when only prevention of oropharyngeal cancer in men is considered [42]. Another commonly mentioned obstacle for sex-neutral vaccination is the high list price of the HPV vaccine. Sex-neutral vaccination is unlikely to be cost-effective at the current list price of the vaccine which varies between 100 and 160 euros per dose in high-income countries. For the costs of vaccination, however, a widely used containment strategy is tendering: health authorities use their purchasing power and the competition in the market of the vaccines to perform procurement procedures. This drives down the vaccine cost and enhances the sustainability of a programme. Experience with hepatitis B vaccines suggests that tendering may lead to strong price reductions over time [43]. Besides, in several Italian regions, tender-based HPV vaccine prices in the first 2 years after the vaccine became available were about 50% lower than the list price [44].

In a recent Dutch cost-effectiveness study [45], in which tender-based vaccine costs were set at about 65 euros for a 2 dose schedule and effects on cervical, vulvar, anal, penile, and oropharyngeal cancers were included, it was calculated that sex-neutral vaccination was cost-effective even when the coverage among girls increased up to 90%. Favourable cost-effectiveness results were also obtained in studies evaluating the vaccination of boys in the Norwegian programme and in the Italian programme when tender vaccine prices were used instead of list prices [46, 47]. All three studies used local input and therefore conclusions do not have to apply to all high-resource settings. However, altogether these findings at least suggest that countries should re-evaluate their economic argument for adopting a girls' only vaccination programme, preferably together with an analysis accounting for country-specific disease burden, country-specific and often tender-based vaccine price, achieved vaccine coverage in the girls' only programme, and the cost of administering vaccines.

Conclusions

The decision to switch from girls only vaccination to sex-neutral vaccination is more difficult to take than the decision to implement a girls' only vaccination programme. This is reflected in the speed at which decisions are taken. About 10 years ago, many countries implemented girls' only vaccination within 1 or 2 years after registration of the vaccine, but only a few of them have switched to sex-neutral vaccination in the meantime. A main argument used to support sex-neutral vaccination is that the burden of oropharyngeal cancer is disproportionate in men, but heterosexual men also benefit from the girls' only programme via herd effects. To facilitate decision-making, mathematical models have been used to assess the additional benefit and cost-effectiveness of vaccinating boys. With respect to sex-neutral vaccination, four conclusions from the models in the literature were that: (1)

sex-neutral vaccination may lead to near elimination of HPV16 and HPV18 when coverage levels are about 80%, (2) a girls' vaccination programme lowers the risk of cancer in men but sex-neutral vaccination still provides substantial extra protection against oropharyngeal and anal cancer when the coverage among girls is moderate, (3) sex-neutral vaccination makes a vaccination programme more robust against sudden changes in vaccine coverage, and (4) sex-neutral vaccination is likely to be cost-effective provided a low vaccine price that is negotiated by health authorities.

Models can be criticized and model-based evidence is graded lower than evidence from randomized trials and cohort studies. Nevertheless, in the coming years, evidence from cohort studies is unlikely to change our current perspective on the effect of vaccination on disease in men. A decision on sex-neutral vaccination will inevitably be taken under a certain degree of uncertainty, but since the incidence of oropharyngeal cancers is currently on the rise in men, such a decision should be both sound and timely.

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Cellular and Molecular Pathology in Head and Neck Cancer

Phil Sloan and Max Robinson

Introduction

Advances in technology and the advent of new therapies are driving the transformation of pathology services to provide molecular testing for head and neck cancer. Pathologists are increasingly playing an active role in clinical trials, particularly in the areas of companion biomarker diagnostic development and testing for patient stratification, biobanking and quality assurance. Higher standards and greater consistency of reporting in pathology is being achieved through the publication of internationally agreed pathology datasets (https://www.iccr-cancer.org/) and the WHO tumour classification [1]. Advances in computation are enabling the linking of datasets, so that patients can be tracked and more holistic information about clinical outcomes can be linked to pathological findings, as well as clinical interventional data. Computational biology and advances in molecular techniques are also enabling large scale studies of cancer cell genomes. Increasingly pathology and genomic services are being integrated and the implementation of digital pathology with the use of emerging artificial intelligence algorithms is allowing diagnostic services to be more effectively managed in a way that improves quality. All of these changes will affect the interactions between pathology and other disciplines involved in managing head and neck cancer.

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International Datasets and the WHO Classification

The International Collaboration on Cancer Reporting (ICCR) has formulated a new set of guidelines for head and neck cancer that are out to consultation at the time of writing. The aim of the ICCR project is to define Core and Optional items for incorporation into standards and datasets for histopathology reporting of cancers. At the same time a narrative text provides guidance and clarification for reporting pathologists, as well as citing relevant source literature. The ICCR guidelines are endorsed by several international and authoritative organisations and are generally aligned to national datasets such as those produced by the Royal Colleges of Pathologists of Australasia (RCPA) and the United Kingdom (RCP), the College of American Pathologists (CAP) and the Canadian Association of Pathologists-Association Canadienne des Pathologists (CAP-ACP), in association with the Canadian Partnership Against Cancer (CPAC) and the European Congress of Pathology (ECP). An advantage of the ICCR guidelines is that they will be freely available worldwide and if adopted universally will facilitate harmonisation of international reporting standards and clinical trials. There are nine sets of guidelines (Table 1) expected to be published in mid-2018.

Much has been written on the AJCC [2] and UICC TNM8 [3] staging manuals. The alignment between the two systems is a useful step forwards and will ensure greater global uniformity in staging. For the first time in the UICC manual, pathological staging and clinical staging are recorded separately for head and neck cancer in certain situations. Further, it is no longer possible to stage patients on the basis of clinical examination alone, as molecular testing for p16 is required for oropharyngeal cancer staging, for example. There are also changes in neck staging that are determined by histologically demonstrated extra-nodal extension. The ICCR guidelines on nodal dissection referred to above will be helpful in providing pathologists with exemplar images and descriptions that will assure higher consistence in pathological staging.

The World Health Organisation classification of head and neck tumours [1] was published towards the end of 2017 and provides an international gold standard that defines and describes the pathology and genetics of disease entities. In several instances diagnosis mandates the use of biomarkers, for example p16 immunohistochemistry for HPV associated oropharyngeal squamous carcinoma, and definitive

Table 1 ICCR head and neck datasets

Nasal cavity and paranasal sinuses
Major salivary gland
Oral cavity
Nasopharynx and oropharynx
Larynx, hypopharynx and trachea
Odontogenic tumours
Ear
Nodal excisions and neck dissection
Mucosal melanoma

pathological diagnosis can no longer be based on morphology alone. Several new entities have been accepted into the classification. Clinical experience of biological behaviour, responses to therapy and clinical outcomes for such rare entities can now be accrued. The most significant change to the 2017 edition is the recognition of human papillomavirus related squamous cell carcinoma as a distinct entity, which closely aligns with the latest UICC and AJCC staging systems. Other major changes involve descriptions of new entities in the sinonasal tract and salivary glands, as well as introduction of a new chapter on tumours and tumour like lesions of the neck. Odontogenic cysts are now included in the WHO classification and some controversial entities have been discarded or more logically classified throughout the text.

Molecular Sequencing

During the last 5 years, several studies have been published that have begun to define the molecular landscape of head and neck cancer. Several studies employing next generation sequencing (NGS), often involving whole exome sequencing have been reported. These studies have identified driver mutations in head and neck squamous cell carcinoma that could be potential targets for therapy. The Cancer Genome Atlas (TCGA) consortium [4] published a comprehensive molecular catalogue on head and neck squamous carcinoma in 2015. Frequent mutations of novel oncogenes that are targets for therapy were not, however, identified [5]. On the other hand, head and neck squamous cell carcinoma is characterized by numerous mutations that create neo-antigens, providing a rationale for the development of immunotherapeutic approaches.

Interestingly, analysis of TCGA data showed a relationship with patient age. Distinct mutational clusters were found in very young (19–40 years) as well as very old (>80 years) patients. In older patients four enriched pathways (Axon Guidance, ECM-Receptor Interaction, Focal Adhesion and Notch Signalling) that are only sporadically mutated in the other age groups were identified. By analogy to biological function the four pathways are supposed to regulate cell motility, tumour invasion and angiogenesis and may lead to less aggressive tumours in older age [6]. However, a disadvantage of NGS is that the mean sequencing coverage of ~80-fold results in limited sensitivity for the detection of tumour subclones. The value of NGS studies is greatly enhanced if clinical cohorts are selected that aim to address specific oncological issues such as the identification of tumours that are chemo/radio-resistant [7]. More studies are needed where the clinical cohorts are precisely defined by stage, subsite, aetiology and therapeutic response in order to elucidate molecular profiles that have clinical utility.

Whole genome sequencing has become progressively less expensive and is an attractive methodology because of the comprehensive genomic coverage that it allows. In the UK, the 100,000 Genomes project is an ambitious programme that aims to create a resource for research that potentially could make a step change in our understanding of the molecular basis of cancer, including head and neck cancer.

Table 2 Head and neck squamous carcinoma subsets [8]

Basal subtype—HPV−, high expression of EGFR/HER, hypoxia
Classical (CL subtype)—low expression of EGFR/HER
HPV+ CL
HPV− CL
Immune/mesenchymal (IM subtype) CD8+ infiltration
HPV+ IM
HPV− IM

Studies involving whole genome sequencing in head and neck cancer have already been published by Keck et al. 2015 [8] and these allowed head and neck cancer to be stratified into three subtypes (Table 2).

In the same year, a meta-analysis of whole genome sequencing data published by De Cecco et al. [9] separated head and neck cancer into six subtypes. Analysis was performed using different criteria to those of Keck et al. and was based on the tumours biological characteristics and de-regulated signalling pathways. De Cecco et al. designated the subtypes as immunoreactive, inflammatory, human papillomavirus (HPV)-like, classical, hypoxia- associated, and mesenchymal. Interestingly, adverse behaviour was associated with the hypoxia-associated and mesenchymal subtypes. These publications used differing but to some extent overlapping criteria. One of the limitations of the computational biology approach to analysis of large genomic datasets is that groups are defined by assumed biological behaviour and validation will be required before application of such data can be extended to individual patients. Nevertheless, WGS studies do indicate that that head and neck cancer has molecular subgroups and it is likely that the heterogeneity observed will be refined and ultimately will allow stratification for prognosis and therapy in the future.

Further analysis and validation studies are required to understand better the data from WGS platforms to allow the findings to translate into precision therapy for individual patients. Once a fuller understanding of the molecular pathology of head and neck cancer is gained, it is likely that the WGS will inform the development of gene panels that would have the advantages of greater sensitivity and specificity, lower cost, better turnaround time, reproducibility and the possibility of testing using formalin fixed paraffin embedded tissue. Alternatively, the cost of whole genome testing is falling year by year and turnaround times are shortening. It may be possible to introduce WGS into routine clinical services in the future. A current limitation is that fresh tissue must be used. Until this is resolved, biopsy samples would have to include adequate representative tissue for conventional histopathological sectioning as well as sufficient fresh tissue for WGS. This is against the trend for smaller biopsies preferred for clinical reasons, and would be highly problematic for laryngeal biopsies or small mucosal cancers, for example those arising in oral potentially malignant disorders. There are many other challenges to the implementation of WGS, not least the development of the bioinformatics analysis algorithms and expertise necessary to interpret sequence data for individual patients. Further, analysis of TCGA data relating to head and neck cancer to date has not identified obvious targets for specific drugs and currently there is no convincing

case for introduction of WGS for head and neck cancer into pathology services [5]. The most promising use of sequencing for head and neck cancer is in the identification of neo-antigens that could be used to develop personalised T- lymphocyte targeted therapy, but more research is needed to demonstrate efficacy.

Stromal Factors

Interplay between the cancer cells and the adjacent stroma is a significant determinant of behaviour and outcomes. Fibroblast heterogeneity is a poorly understood process but single cell genomic studies of head and neck cancer reveal two subpopulations of fibroblasts, one of which expresses smooth muscle actin (SMA) and one of which does not. The SMA expressing fibroblasts represent myofibroblasts whilst the other population represents normal and senescing fibroblasts. In vitro studies show that fibroblasts can be induced to express smooth muscle actin by TGF beta, indicating a reversible phenotype [10]. Furthermore in vitro, three fibroblast subpopulations can be identified that have distinctive genetic profiles. These are fibroblasts, myofibroblasts and senescent fibroblasts [11]. Importantly, fibroblast populations appear to have prognostic value [12]. Further studies of the tumour microenvironment are likely to provide insights into complex biological interactions that underpin cancer invasion and metastasis.

Matrix macromolecules are also an important determinant of cancer cell behaviour. In tongue carcinoma, the abundance of the tenascin C has been shown to be a significant prognostic factor [13]. In contrast to fibronectin which mediates fibroblast adhesion, tenascin C has been shown to have an anti-adhesive effect, facilitating cell migration in vitro [14]. In normal murine and human dorsal lingual epithelium, tenascin C has a distinctive pattern of distribution being located at the tips of the connective tissue papillae but not along the bases of the rete processes [15]. This distinctive pattern of distribution may relate to epithelial stem cell distribution and amplification divisions, facilitating cell flow along basement membrane or though cell signalling mechanisms. In a cohort of early stage tongue cancers, poor cumulative survival was associated with the presence of abundant stromal tenascin and fibronectin, whereas cellular tenascin did not distinguish the groups. This might be explained by the assembly and accumulation of tenascin in the extracellular matrix [13]. In addition to the matrix factors, epithelial-mesenchymal transition is a recognised process in head and neck cancer biology and elucidation of the pathways involved may lead to identification of future therapeutic targets.

Immunological Landscape

The introduction of immunotherapy into head and neck cancer practice offers a new range of therapeutic options. There is considerable interest in the use of programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors in head and