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Overview

Advancing Care for Head and Neck Cancers in a Multidisciplinary Tumour Board in the East

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Abstract

Managing head and neck cancers is an excellent example of the importance of teamwork, with head and neck surgeons, clinical oncologists, radiologists, pathologists and other allied health professionals specialised in this disease site working together. The reliable imaging and dedicated pretreatment work-up entailing the comprehensive anatomical description of tumour involvement by the radiologists, the expertise of surgeons in performing en-bloc gross tumour resection, the uneventful speedy postoperative rehabilitation and recovery by the speech therapists and nutritionists, as well as the dedicated treatment planning of clinical oncologists in delivering precise preoperative or postoperative (chemo)radiotherapy to maximise the therapeutic potentials are the pillars of treatment success. A multidisciplinary tumour board involving all of these key players is essential to provide the highest level of recommendation based on evidence-based medicine and to bring patients new hopes and the best chance of cure. This review illustrates the seamless collaborative teamwork within a well-established multidisciplinary tumour board in managing one of the most intractable cancers in the East, taking enlightenment and inspiration from the West.

Key words: Head and neck cancers; multidisciplinary management; tumour board

Introduction

Head and neck cancers (including lip, oral cavity, salivary glands, oropharynx, nasopharynx, larynx and hypopharynx) are among the most common malignancies in the world [1]. Yet they are also among the most intractable cancers, rarely amenable to effective curative treatment because of their close proximity to important critical structures in the head and neck and the central nervous system. Patients also have a suboptimal performance status owing to the profound adverse effects of chronic tobacco and alcohol consumption and a relatively malnourished physical status from the obstructing tumours in the upper aerodigestive tract limiting oral intake. In the past, surgery was usually the most upfront treatment, as most patients are usually referred to see surgeons [2]. The lack of advanced, effective and tolerable treatment by traditional chemotherapy and radiation techniques was also probably another reason why oncologists' opinions were not sought before the operation. In addition, in some countries/regions, government reimbursements for medical expenses frequently go to the treating institution/department. Oncologists are often consulted for postoperative treatment due to positive resection margins, radical concurrent chemoradiation for either surgically or medically inoperable

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diseases or just for palliative chemotherapy/radiotherapy for extremely locoregionally advanced or metastatic disease.

Now there are state-of-the-art radiation techniques, including intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy, stereotactic radiotherapy, tomotherapy and proton therapy, concurrent chemoradiation, and a combination of radiation therapy and targeted therapy for head and neck cancers [3–6]. Radiation therapy has become the most important non-surgical modality, used in a half of all cancers. Meanwhile, the development of new and enhanced surgical techniques, including modified radical neck dissection, sentinel nodal sampling, as well as robotic surgery, also allows more personalised, precise and safe surgery with speedy postoperative recovery [7–10]. Of equal importance, the availabilities of more sensitive and accurate imaging modalities, like magnetic resonance imaging (MRI), positron emission tomography with integrated computed tomography (PET-CT) and other functional imaging tools, together with the novel imaging sequences and interpretation algorithms, like radiomics, radiogenomics and bioinformatics, can better help us differentiate tumours from non-malignant or post-treatment changes [11–13]. All of these new discoveries and advances undoubtedly enable surgeons and oncologists to judge the resectability and the extent of surgery, and consider accurate target contouring for subsequent radiation therapy and decide if additional treatment is necessary.

With this recent drastic and explosive emergence of new surgical, non-surgical and imaging advances, the 'one disease managed by one discipline' concept no longer exists. Instead, a close and intimate collaboration among all specialties is urgently indicated to avoid misdiagnosis and treatment delays, to maximise patients' treatment outcomes and safety, and allow knowledge exchange and future research collaboration. The upsurge in demand for more personalised treatment by the explosive knowledge of tumour genomic and radiomic/radiogenomic profiles from next-generation sequencing and growing patient requests drive the establishment of a multidisciplinary tumour board (MTB).

The concept of an MTB became apparent about 20 years ago, when it was envisaged that a single treatment modality could not further escalate and improve the therapeutic ratio without the expense of treatment-related morbidity and mortality. The MTB was first established in academic and tertiary cancer centres in the USA and then in Europe, where experienced surgeons, oncologists, radiologists and pathologists were readily available to conduct randomised controlled trials on multimodality treatment and to carry out sophisticated and complicated surgical, radiotherapeutic and imaging procedures in a real-world routine clinical setting [14–16]. An MTB can offer the highest level of recommendation to individual patients based on the most recent evidence-based medicine and the availability of resources at the treating institution. It also reflects shared decision and risk management shouldered by all the stakeholders. If the team thinks that the treating institution cannot execute such a management plan because of inherent deficiencies, it will refer the patients to other treatment centres equipped with such expertise and resources. A good illustration would be referring a child to proton therapy for his/her uveal melanoma if there is no such treatment facility in the referring institution. An ideal MTB should also regularly carry out quality assurance to constantly evaluate the percentage of treatment recommendations ultimately executed and identify the reasons for treatment deviance, which can lead to further enhancement of the MTB's structure and treatment execution and obviously improve team dynamics [17].

Although it persistently prevails in the West, an MTB is a critical rarity in the East for numerous reasons, some of which were mentioned above. Our institution has had a head and neck MTB for 10 years. It takes place weekly in the early morning before surgeons carry out their operations. With the valuable input and exchange of opinion among all clinicians from different specialties, a personalised treatment decision is made by this credible and responsible team who will steadfastly and swiftly execute this decision without treatment delay and compromise of treatment outcomes. On top of that, clinical oncologists at our institution, who are the gatekeepers of oncological treatment for most solid tumours, are licensed and competent to deliver radiation therapy, chemotherapy, targeted therapy and even immunotherapy, which certainly obviates the chance of miscommunication between radiation oncologists and medical oncologists, as may occur in other parts of the world when it comes to considering concurrent treatment with chemotherapy, targeted therapy and even immunotherapy, or treatment interruption secondary to significant toxicities.

As managing head and neck cancers is complex and sophisticated, a detailed preoperative assessment, including a physical fitness evaluation, pretreatment imaging and the most crucial issue on the choice of treatment by either a single modality or a multimodality approach, must be thoroughly considered and carried out before the management decision is made. A head and neck MTB is definitely essential; it should consist of surgeons, oncologists, radiologists, pathologists and other allied health professionals, who are the key players of the whole management team to make an individualised treatment plan for every single patient. This effective communication and resource interface among these specialties should make their clinical judgement and recommendation based on the disease stage, extent of tumour involvement, expertise and resource availability in the treating institution, as well as the trust and support of all of these key players. More importantly, the treatment recommendation should be continuously reviewed and revised during the whole treatment and post-treatment period, as everything, including the patients, tumours and equipment, can change drastically. An immediate contingency plan should be devised in case the original treatment algorithm is unexpectedly breached. Here we shall review our experience to highlight the importance of the multidisciplinary management of head and neck cancers based on each disease site,

with examples, which has certainly escalated the level of patient care in our head and neck cancer patients.

Lip Cancer

Lip cancer usually presents very early due to easy recognition and can lead to physical and psychological disfigurement. In addition, it rarely metastasises to regional nodes and distant sites. Surgery is the standard treatment for early small tumours. However, postoperative reconstruction is often necessary for large tumours, owing to difficult skin and soft tissue apposition in the primary wound closure. As there is no good body tissue that can fully cosmetically mimic and replace the lip, significant disfigurement may occur if a large defect has to be reconstructed. On the other hand, brachytherapy is certainly an excellent alternative to surgery, providing comparable tumour control but with better preservation of the patient's cosmetic and psychological outcomes, which is preferred by patients and accepted by surgeons through discussion in the MTB (Figure 1).

Oral Cavity Cancer

Comprehensive diagnostic and pretreatment imaging investigations are necessary as submucosal tumour can be missed by conventional imaging (Figure 2). Oral cavity cancer, especially tongue cancer, can invade and spread rigorously to adjacent structures and regional cervical nodes. Surgery is usually the upfront treatment modality, whereas radiation therapy/chemotherapy is usually used following operations, especially when the tumour demonstrates bony erosion to the mandible or nasal cavity/paranasal sinuses [18]. In particular, selective ipsilateral neck dissection at the time of primary surgery for node-negative disease confers an overall survival benefit compared with therapeutic neck dissection at the time of neck relapse, as shown by a randomised controlled trial in India [19].

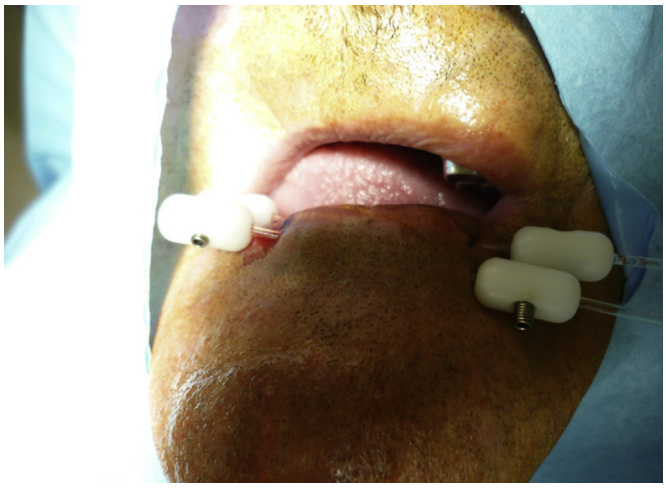

Fig 1. Image of a patient who had applicator tubes inserted for radical brachytherapy for early squamous cell carcinoma of the lower lip.

Accurate and perhaps generous target delineation and contouring for postoperative radiation therapy is highly desired to encompass subtle subclinical invasion to the gingival sulci and periodontal structures, as in-field or marginal recurrence, especially at the infratemporal fossa, is the most common site of treatment failure [20,21]. Extracapsular spread and positive/close resection margins are significant predictors of failure of locoregional control. In addition, an expert surgical reconstruction and rehabilitation team is highly sought after for physical and functional reconstruction so that patients can resume feeding and other physical functions, including degustation, phonation, articulation and speech, as quickly as possible. An MTB can more easily engage all disciplines to formulate a detailed plan of immediate and long-term postoperative rehabilitation.

Laryngeal and Pharyngeal Cancers

Laryngeal cancers usually present earlier than pharyngeal/hypopharyngeal cancers, as hoarseness due to impairment of vocal cord mobility is easy to detect. Early stage laryngeal cancers can be effectively managed by surgical (laser excision or partial laryngectomy) or non-surgical modalities [22–28], with a local control rate between 75 and 100% at 5 years. Radiation therapy for early laryngeal cancers or carcinoma *in situ* can either be used as upfront or salvage treatment after failure of surgery or laser therapy [22,29].

The contemporary management of advanced laryngeal and hypopharyngeal cancers is still diversified and challenging, owing to the heterogeneity of tumour biology and presentation and the rapid and sudden change in a patient's clinical condition when the tumours progress. Surgery followed by postoperative radiation ± chemotherapy was the standard treatment for the past 30 years. The addition of concurrent chemotherapy to radiation therapy was shown to improve overall survival in those patients who suffered from extracapsular nodal extension and positive resection margins [30–32]. With improved efficacy of chemotherapy, laryngeal preservation after induction chemotherapy and/or radiation becomes a possibility in some patients, leading to a better quality of life [33–35]. The better sparing of the salivary glands, pharyngeal constrictors and other structures involved in swallowing by modern radiation techniques also resulted in a significant quality of life improvement [36–38].

Treatment becomes more complicated and perplexing to the oncologists in the real-world setting even within the context of non-surgical treatment of locally advanced laryngeal and hypopharyngeal cancers. A phase III randomised controlled trial conducted in India comparing high-dose cisplatin every 3 weeks with weekly low-dose cisplatin revealed a superior locoregional control albeit with more toxicities [39]. Other previous studies have revealed that the addition of induction chemotherapy to concurrent chemoradiation did not translate into better survival than concurrent chemoradiation alone [40–44].

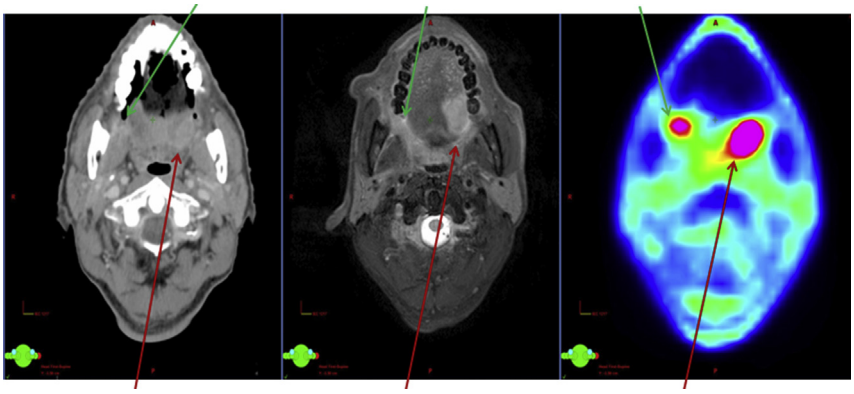

Fig 2. Pretreatment images of a patient diagnosed with clinically apparent squamous cell carcinoma of the right retromolar trigone. Magnetic resonance imaging (middle panel) and positron emission tomography (right panel) identified a clinically occult T2-hyperintense and hypermetabolic tumour at his left tongue base, respectively, which was just vaguely seen on his contrast-enhanced computed tomography scan (left panel). A subsequent left tongue base biopsy confirmed synchronous squamous cell carcinoma.

Notwithstanding, all of these studies did not consider human papillomavirus (HPV)-positive oropharyngeal cancer (OPC) as a separate entity, which is evolving at a rapid pace [45]. A recent retrospective review indicated that induction chemotherapy followed by concurrent chemoradiation in HPV-positive OPC with low neck/N3 lymphadenopathy produced better 3-year distant metastasis-free survival and progression-free survival when compared with concurrent chemoradiation alone [46]. In the real world, oncologists are very pressed for time and are sometimes tempted to offer one to two cycles of induction chemotherapy before concurrent chemoradiation, as the waiting time required for radiation treatment planning is at least 3–4 weeks before treatment commencement, during which time the patient's condition and nutrition can deteriorate because of rapid tumour enlargement and obstruction.

The discovery of HPV-positive OPC has shed light on the shift in management paradigms and prognosis as compared with HPV-negative tumours. The better prognosis of HPV-positive OPC has led to the implementation of a distinct eighth edition of TNM staging classification from HPV-negative OPC [47,48]. In addition, the more favourable response to chemoradiation in HPV-positive OPC has also prompted the West to design de-escalation or more personalised studies from both the surgical and oncological perspectives. It is also now an increasing concern of surgeons and oncologists in the East because of the rising incidence of HPV-positive OPC [49–51].

When traditional radiotherapy/chemotherapy was still given, salvage surgery after failure of radiation with or without chemotherapy did not really prolong survival, as patients' physiques were severely compromised by malnutrition, serious neck fibrosis in the operative field and poor wound healing due to a deficient blood supply following chemoradiation [52,53]. However, survival has greatly improved recently with the latest technological advances in surgery and radiation therapy. Salvage surgery following locoregional failure of prior radical chemoradiation has been found to improve survival, as reported in the recent large retrospective study of 1000 patients treated with modern radiation techniques (i.e. IMRT) as either radical or postoperative treatment. In addition, oligometastatic disease (1 versus $\geq$2) was also associated with better overall survival following distant metastasis [54].

Given such wide diversity, availability and emergence of numerous surgical and oncological treatment options, especially in an academic tertiary referral cancer centre, an MTB is highly desirable to freely discuss the patient's condition, their comorbidities, the side-effects of treatments and the expertise within the MTB in order to make the best unbiased decision. Every member in the MTB should not feel guilty or frustrated but be prepared for the second priority in case the top recommendation cannot be implemented.

Nasal Cavity and Paranasal Sinus Cancers

Most of the tumours in the nasal and paranasal cavities demonstrate overt bony erosion, for which surgery rather than non-surgical treatment is a higher priority as first-line treatment. Also, most tumours are not sensitive to radiation therapy or chemotherapy as induction or concurrent treatment, which may further delay or jeopardise the chance of a curative surgery. The rule of thumb of treating paranasal sinus tumours is therefore upfront surgery followed by radiation and/or chemoradiation depending on the histological types and resection margin status. Exceptions may be some chemosensitive or radiosensitive tumours, e.g. olfactory neuroblastoma and perhaps SMARCB1 (INI-1)-deficient sinonasal carcinoma, for which preoperative or radical chemoradiation is worth considering, and surgery should be reserved as salvage treatment, after through discussion within the MTB and the patient regarding the risks and benefits [55,56]. This was illustrated in one of our recent patients whose extremely locally advanced SMARCB (INI-1)-deficient sinonasal carcinoma invading the lamina papyracea and compressing the medical rectus and superior oblique muscles demonstrated complete response after induction chemotherapy and

radical chemoradiation (Figure 3). He was exempt from orbital enucleation and remained disease free without visual acuity and visual field impairment for almost 1 year. The importance of effective, continuous and unbiased communication among surgeons, oncologists, pathologists, patients and their relatives within the MTB and the combined clinics should be acknowledged.

Nasopharyngeal Cancers and Other Skull Base Tumours

Nasopharyngeal cancers (NPC) and other skull base tumours are perhaps the tumours that require the top level of collaboration by surgeons, oncologists, radiologists and pathologists. Although NPC are extremely responsive to initial radiation therapy or concurrent chemoradiation, about 30% recur locoregionally within 5 years. By virtue of their close proximity to the major nerves, vessels and other important nervous/bony structures in the skull and the central nervous system, which have previously received a high dose of radiation, a multimodality approach is definitely indicated for locoregionally recurrent diseases.

For early recurrent disease, either surgery or re-irradiation is an acceptable treatment option [57–60]. Robotic-assisted or endoscopic nasopharyngectomy can even be considered for small centrally located recurrent disease [61,62]. They show comparable local control despite a few complications as compared with the open surgical approach. Previously locally advanced rT3/T4 NPC with extensive skull base and intracranial invasion are usually fatal as they are usually, if not always, beyond resectability. Second radical radiotherapy (IMRT, tomotherapy, SBRT) with or without chemotherapy may occasionally provide durable local control at the expense of significant long-term complications, like massive bleeding, carotid pseudoaneurysm, aspiration pneumonia, etc. [59,60]. Palliative chemotherapy could only modestly prolong survival. With growing expertise, surgery becomes feasible in the current era. Trust between surgeons and oncologists has to be built up in the MTB to bring new hope to these patients by introducing new surgical treatment options [63,64]. Our institution has introduced staged extracranial/intracranial vascular bypass followed by craniofacial resection for selected rT3/T4 NPC that has encased the internal carotid artery [62]. After bypassing the tumour-encased portion of the internal carotid artery, the recurrent NPC can be resected with a wide resection margin and little perioperative complications.

For those inoperable rT3/T4 NPC, a second course of radiation therapy with new techniques can be considered. A hyperfractionated IMRT delivering two daily fractions (1.2

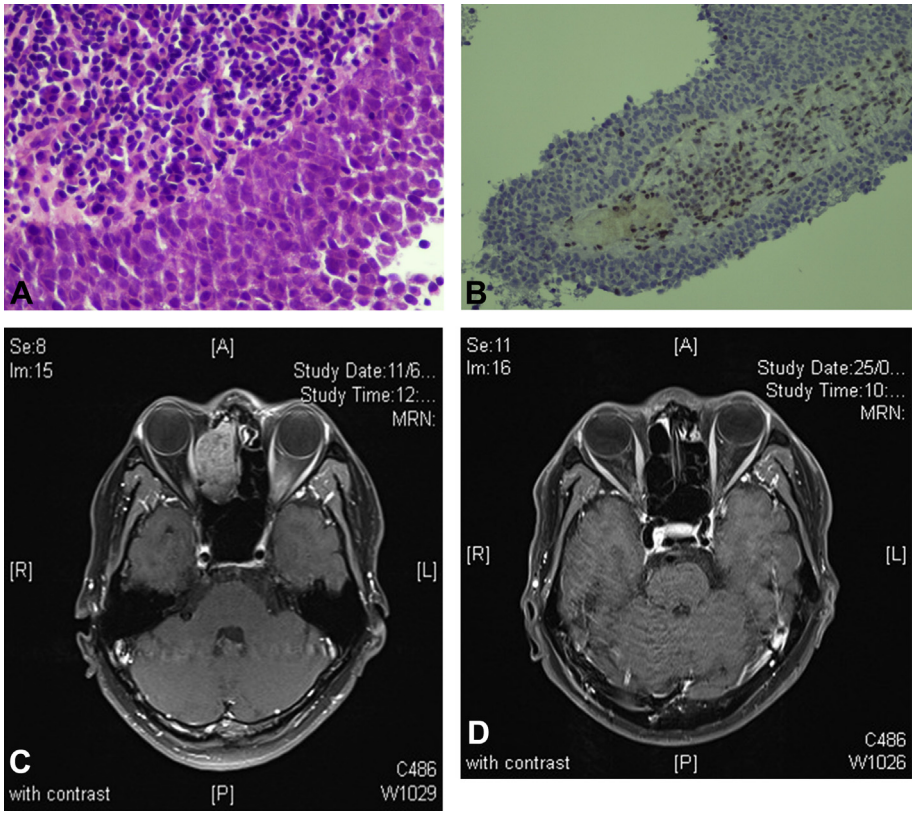

Fig 3. (A) Formalin-fixed paraffin-embedded section from a patient recently diagnosed with SMARCB (INI-1)-deficient sinonasal carcinoma showing the presence of poorly differentiated carcinoma with a basaloid cell pattern with (B) INI-1 deficiency in the background of the positively stained lymphoplasmacytic cells in the core. (C) Pretreatment magnetic resonance imaging showing a bulky tumour at the right ethmoid sinus that eroded the lamina papyracea and compressed the medial rectus muscle. (D) A complete response after two cycles of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil and radical cisplatin-based concurrent chemoradiation.

Gy per fraction up to 64.8 Gy) with concurrent weekly cisplatin (with or without induction chemotherapy) has proven feasible and safe for these bulky inoperable diseases that have already received an extremely high dose of radiation therapy as their first course of treatment [65]. Another approach would be induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil followed by concurrent radiation therapy with weekly cetuximab, as reported in our multicentre phase II prospective study [66].

As even modern imaging with MRI and PET-CT may not confidently differentiate recurrent disease from post-treatment changes, radiogenomics is becoming an interesting topic in NPC. Radiogenomics is a specific and distinct scientific field that addresses possible associations between genetic alterations and normal tissue toxicities after radiation therapy. Substantial progress has been made in this field over the past decade. Radiogenomic studies in NPC are currently underway [67–73]. However, they have been limited by small sample sizes and the absence of robust internal and external validations. Our institution has started radiomics and radiogenomics studies and identified that some patterns are associated with a worse outcome after chemoradiation. Using a radiomics approach, where quantitative imaging parameters can be derived from tumour regions based on shape, texture and higher-order features, it has been shown in several papers that a radiomics model is associated with outcomes such as progression-free survival and overall survival [74–78]. For example, in our study, we have built a radiomics model using 217 patients to predict early progression of non-metastatic NPC after IMRT, leveraging machine learning statistics using a support vector machine that was externally validated on an independent cohort ($n = 60$). The final model achieved an AUROC of 0.80 in both the discovery and independent validation cohorts (unpublished data).

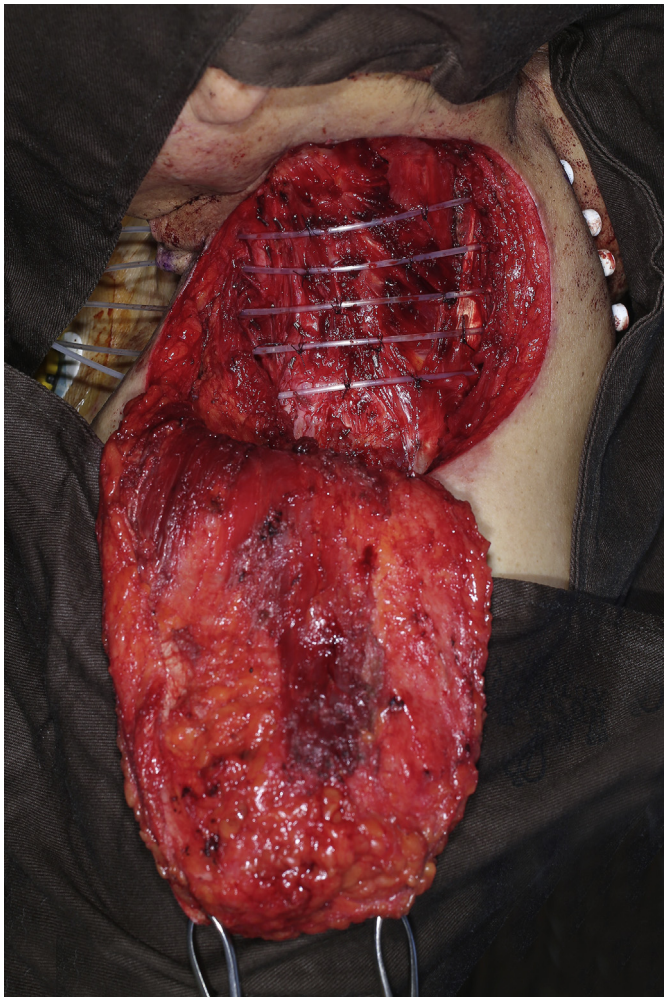

Fig 4. Insertion of afterloading brachytherapy tubes at a high-risk tumour bed next to the left subclavian artery followed by flap reconstruction with latissimus dorsi and postoperative high dose rate brachytherapy in a patient with radiation-associated high-grade sarcoma after previous radical chemoradiation for nasopharyngeal carcinoma.

Radiation-associated Second Malignancies

Radiation-associated second malignancies are uncommon, but they pose a particular concern to young long-term survivors. The standardised incidence rate was reported to be 2–3% [79–81]. It was observed that the incidence with IMRT was nearly double that with older radiation techniques, primarily because of the larger volume of normal tissues exposed to low-dose radiation [82]. Another postulation is that there are more survivors after IMRT in the modern era. Diagnosis, even with modern imaging modalities, is extremely challenging, as they can mimic benign post-treatment complications, like osteoradionecrosis or fibrosis. Surgery followed by reconstruction is the standard of care, although postoperative high dose rate interstitial neck brachytherapy with 30–35 Gy in twice daily fractions over 1 week for those tumours adhered to carotid arteries aiming at better local control has also been carried out in our institution for more than 20 years [83,84] (Figure 4). A dedicated surgical, oncological and radiological team in the MTB must be present in order to carry out the subsequent resection, interstitial brachytherapy and flap reconstruction.

Management of Treatment-related Complications after Chemoradiation

Temporal lobe necrosis and osteoradionecrosis after prior radical chemoradiation is a concern for long-term NPC survivors, oncologists and surgeons. They are usually underestimated and common symptoms like headache and dizziness are often neglected. Life-threatening complications, including leakage of cerebrospinal fluid and central nervous system infections with brain abscess, can be observed in advanced conditions. A dedicated imaging work-up with contrast MRI scans and PET-CT is often necessary to help distinguish them from NPC recurrence (Figure 5). Although medical treatment with pulse steroid or bevacizumab for temporal lobe necrosis and

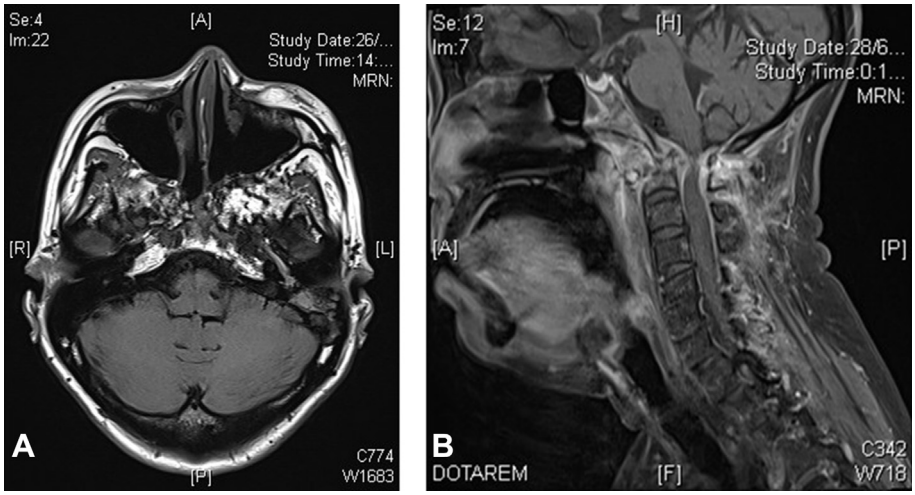

Fig 5. Preoperative magnetic resonance images in (A) axial and (B) sagittal planes showing extensive osteoradionecrosis of the clivus and skull base in a patient previously treated with radical radiation therapy for nasopharyngeal carcinoma.

pentoxifylline and tocopherol with or without clodronate for osteonecrosis can relieve early conditions, endoscopic or open surgical debridement with or without flap reconstruction is indicated and beneficial to reduce seizures, bleeding, pain and infection, as reported previously [85–88]. Again, a broad and extensive discussion within the MTB is warranted before such ultra-major and complex surgery is considered.

Speech, Swallowing and Dietary Rehabilitation

Surgery, radiation therapy and chemotherapy inevitably bring serious sequelae to speech, swallowing and nutrition of almost all head and neck cancer patients. These complications do not just affect the whole treatment schedules, but also impact significantly on the patient's quality of life and physical health in the long term [89]. Previous studies have shown that most cancer patients suffer from weight loss of more than 5% and malnutrition can occur in head and neck cancer patients who just receive radiotherapy alone, which can lead to a worse treatment outcome [90,91]. An increase in nutritional intake was previously shown to be correlated with an improved quality of life in patients with head and neck and gastrointestinal cancer. Recent studies revealed that individual dietary counselling before and during radiotherapy could reduce weight loss and malnutrition in patients with head and neck cancers [92,93].

The United Kingdom National Multidisciplinary Guidelines recommend that every head and neck cancer patient should have a pretreatment clinical, speech and swallowing assessment [94,95]. They also recommend a detailed nutritional screen for every patient before treatment, as well as continuous advice on nutritional intake and dietary intervention during and after treatment [96]. In Hong Kong, apart from a pretreatment assessment by speech therapists and dieticians, all NPC patients must have a pretreatment pure-tone audiography assessment for hearing ability, as well as a comprehensive ear, nose and throat examination by our otorhinolaryngologists to evaluate if there is any serous otitis media secondary to Eustachian tube obliteration by NPC, and any pretreatment swallowing difficulties, which prompt earlier surveillance if feeding tube dependence during and after treatment is indicated. Also, dental surgeons are always consulted before treatment if dental extraction is required to reduce the chance of subsequent dental caries or periodontal diseases. They also continuously follow-up our patients for early detection of osteonecrosis following surgery and radiation therapy. Oromaxillofacial surgeons are also important in correcting teeth malalignment and customising obturator prostheses to patients following mandibular/maxillary resection in an attempt to restore articulation, mastication and quality of life following surgery [97].

Conclusion

The success of efficacious treatment and swift recovery for head and neck cancer patients relies heavily on the intimate and ceaseless collaboration among all crew members of a head and neck oncology team. A dedicated and efficient MTB that makes a shared and unanimous evidence-based management decision and personalised treatment recommendation is crucial so that it can be duly offered to every patient without procrastination. The treatment progress should also be continuously reviewed and regular revisions of treatment decisions in the MTB have to be made as these patients are fragile and susceptible to drastic changes in body functions during the course of their treatment. It is encouraging to see that the MTB is gradually gaining popularity in the East after learning from the West. It is also hoped that a tailor-made clinical treatment and rehabilitation pathway can be designed for every individual patient through this platform so that the physical, psychological and quality of life outcomes can be maintained and secured.

Conflict of interest

The authors declare no conflict of interest.

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