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Review

Current Management Strategy of Nasopharyngeal Carcinoma

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Nasopharyngeal carcinoma is an unique head and neck cancer. It is common among the southern Chinese and is closely associated with the Epstein Barr virus (EBV). To diagnose the disease in its early stage is infrequent as the symptoms are usually trivial and patients only present in late stages. Testing the blood for elevated EBV DNA has now become a screening test for the high risk group of patients, aiming to diagnose the disease in its early stages. Imaging studies, positron emission tomography scans in addition to clinical examination provide information on the extent of the disease. The confirmation of the disease still depends on endoscopic examination and biopsy. Radiotherapy with or without chemotherapy has been the primary treatment modality. The application of intensity modulated radiotherapy and the use of concomitant chemoradiation have improved the control of nasopharyngeal carcinoma together with the reduction of long term side effects. The early detection of residual or recurrence tumor in the neck or at the primary site has allowed delivery of salvage treatment. The choice of the optimal surgical salvage, either for neck disease or primary tumor depends on the extent of the residual or recurrent disease. The outcome of these patients have improved with the application of the appropriate surgical salvage.

Key Words. *Nasopharyngeal carcinoma, Diagnosis, Management, Radiotherapy, Chemotherapy, Surgical salvage*

INTRODUCTION

A group of 14 patients suffering from nasopharyngeal carcinoma (NPC) was first reported in 1901 (1) and the clinicopathological features of 114 patients was published in 1941 (2). This malignancy is a squamous cell carcinoma with varying degrees of differentiation arising from the epithelial lining of the nasopharynx. It is most frequently seen at the pharyngeal recess, the fossa of Rosenmüller, situated medial to the medial crus of the Eustachian tube opening in the nasopharynx (3, 4).

NPC is common in southern China, especially the province of Guangdong. The recent reported incidence of NPC among men and women in Hong Kong (geographically adjacent to Guangdong province) was 20 to 30 per 100,000 and 15 to 20 per 100,000 respectively (5). There is also increased incidence in northern Africa and the Inuits of Alaska (6), but it is an uncommon disease in most countries, and its age-adjusted incidence for both sexes is less than 1 per 100,000 (5). The incidence of NPC remains high among Chinese who have immigrated to other parts of Asia or North America, but is lower among Chinese born in North America than in those born in southern China (7, 8). This suggests that genetic, ethnic and environmental factors might have a role in the etiology of this malignancy.

SYMPTOMS AND SEROLOGICAL DIAGNOSIS

NPC patients frequently present with one or more of 4 groups of symptoms, they are firstly nasal symptoms such as epistaxis, nasal obstruction and discharge. This is related to the presence of tumor mass in the nasopharynx; secondly, otologic symptoms such as deafness and tinnitus related to the dysfunction of the Eustachian tube caused by the latero-posterior extension of the tumor to the paranasopharyngeal space. Thirdly, cranial nerve palsies, commonly 5th and 6th cranial nerves, this is associated

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with the superior extension of the tumor leading to skull base erosion; the patient might experience headache, diplopia, facial pain and numbness. Fourthly, neck masses, they usually appear in the upper neck. General symptoms of malignancy such as anorexia and weight loss are uncommon in NPCs, and distant spread should be suspected when these symptoms are present.

A retrospective analysis of 4,768 patients identified the symptoms at presentation as neck mass (75.8%), nasal (73.4%), aural (62.4%), headache (34.8%), diplopia (10.7%), facial numbness (7.6%), weight loss (6.9%), and trismus (3.0%). The physical signs present at diagnosis were enlarged neck node (74.5%), and cranial nerve palsy (20.0%). The cranial nerves most commonly involved were the fifth, sixth, third and twelfth (9, 10). The presenting symptoms in young patients were in general similar to those in adults (11).

Unfortunately, as the nasal and aural symptoms are non-specific and also it is a full clinical examination of the nasopharynx is not easy, the majority of NPC patients are only diagnosed when the tumor has reached an advanced stages.

Where patients present with symptoms of NPC, they should be clinically evaluated for physical signs of NPC. A positive Epstein Barr virus (EBV) serology test will give further grounds for suspicion and elevated copies of EBV DNA in the serum would justify an endoscopic examination and a biopsy from the nasopharynx.

A definitive diagnosis of NPC requires a positive biopsy taken from the tumor in the nasopharynx, supported either by its visualization in the nasopharynx.

PATHOLOGY

NPC in early years was called lymphoepithelioma, as the malignant epithelial cells of the nasopharynx frequently intermingled with lymphoid cells in the nasopharynx, giving rise to the term lymphoepithelioma (12). Electron microscopy studies however have determined that these tumor cells are of squamous origin and the undifferentiated carcinoma is a form of squamous cell carcinoma with minimal differentiation (13, 14).

The histological classification of nasopharyngeal carcinoma proposed by the World Health Organization (WHO) in 1978 categorized tumors into three types. Type I were the typical keratinizing squamous cell carcinomas, similar to those found in the rest of the upper aerodigestive tract. Type II included non-keratinizing squamous carcinomas and type III were the undifferentiated carcinomas (15). In recent years, an alternative classification was proposed and this divided NPC into two histological types, namely squamous cell carcinomas (SCCs) and undifferentiated carcinomas of the nasopharyngeal type (UCNTs) (16). The second classification is found to correlate with Epstein Barr virus serology tests. Those patients with SCCs have a lower EBV titer, while those with UCNTs have elevated titers. This classification is more applicable for epidemiological research and has also been shown to have a prognostic bearing. The undifferentiated carcinomas have a higher local tumor control rate with therapy, and a higher incidence of distant metastasis (17, 18). In North America, tumor histology in 25% of patients is Type I, 12% Type II, and 63% Type III. The corresponding histological distribution in southern Chinese patients is 2%, 3%, and 95% respectively (19).

EBV is consistently detected in NPC patients from regions of high and low incidence. Using EBV-encoded RNA (EBER) *in situ* hybridization, EBER signal was present in virtually all tumor cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbor EBV, suggesting the EBV infection occurs in the early phases of carcinogenesis (20). Specific EBV latent genes are consistently expressed within the NPC tumors and also in early, dysplastic lesions.

Because of this association with EBV, EBV serology has been used for population screening. In a study conducted in Wuzhou (Guangxi province, China) in the early 1980s, 1,136 individuals identified as IgA/VCA-positive received regular clinical examinations of the nasopharynx and neck for a period of four years. During this follow-up period 35 NPC cases were detected, most of which (91.5%) were diagnosed early, at either stage I or stage II. The annual detection rate of NPC for this group was 31.7 times higher than for the population as a whole (21). The predictive value of EBV serology for NPC was noted again recently. In this study, the initial EBV serology of 9,699 study subjects was cross-checked against the cancer registry and death registry over a 15-yr period. It was found that the longer the duration of follow-up, the greater the difference in the cumulative incidence of nasopharyngeal carcinoma between seropositive and seronegative subjects (22).

EPSTEIN BARR VIRUS DNA

Malignant cells have a high turnover rate and on cell lysis there is an increased EBV DNA released into the blood. These circulating free EBV DNA can now be detected by polymerase chain reaction (PCR) in patients with NPC (23). The increased number of copies of EBV DNA found in the blood during the initial phase of radiotherapy suggests that the viral DNA was released into the circulation after cell death (24). The quantity of free plasma EBV DNA as measured by real time quantitative PCR has been shown to be related to the stage of the disease. The detection of EBV DNA has been increasingly used for the diagnosis of NPC. For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options (25). The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival (26, 27). There was a study reporting that the levels of post-treatment EBV DNA when compared with pretreatment EBV DNA had a better prediction

for progression-free survival (28). When EBV DNA was employed together with IgA against viral capsid antigen of Epstein Barr virus increases the sensitivity of early diagnosis of nasopharyngeal carcinoma (29). Elevated levels of EBV DNA were only detected in 67% of patients with locoregional recurrence when the recurrence volume was small (30).

IMAGING STUDIES

Clinical examination, including endoscopic examination of the nasopharynx can provide valuable information on mucosal involvement and local tumor extension. It however cannot determine deep extension of the tumor such as skull base erosion and intracranial spread.

Cross-sectional imaging has revolutionized the management of NPCs. In terms of contribution to staging, CT can identified the paranasopharyngeal extension as one of the most common modes of extension of NPC (31), and perineural spread through the foramen Ovale as an important route of intracranial extension. Perineural spread through the foramen Ovale also accounts for the CT evidence of cavernous sinus involvement without skull base erosion (32).

Magnetic resonance (MR) is better than computed tomography (CT) for displaying nasopharyngeal soft tissues and differentiating tumor from soft tissues, MR is also more sensitive at evaluating retropharyngeal cervical nodal metastases (33) and also bone marrow infiltration (34) MR, however, is of limited effectiveness in evaluating bone details, and CT should be performed when the status of the base of the skull needs evaluation (35).

Imaging of distant metastases at diagnosis is less successful, and a number of studies have concluded that bone scans (36), liver scintigraphy (37), abdominal ultrasonography (38), and marrow biopsy (39) are of little value in routine staging, The role of positron emission tomography (PET) in the detection of distant metastases in NPC and other malignancies has been established (40). It has been reported that PET is more sensitive than CT and MR at detecting residual and recurrent tumors in the nasopharynx (41).

Cross-sectional imaging displays precisely the primary tumor extent. This enables radiotherapy treatment to be administered more accurately and effectively, and thus improved the outcome (42). It has recently become possible to get even better results with intensity modulated radiotherapy (IMRT), which makes use of composite CT-MRI targets (43), and this enables radiotherapy to be targeted even more accurately onto tumors and to spare adjacent normal tissues.

STAGING

There were a few staging systems for NPC. The American Joint Committee (AJC)/International Union Against Cancer (UICC) system is preferred in Europe and America (44), while Ho's system is frequently used in Asia (45, 46). In the latter, its nodal classification has incorporated its prognostic significance, but its stratification of the T stages into 5 sectors differs from other staging systems. The development of a revised staging system in the past decade was motivated by the desirability of incorporating experiences gained from various centers around the world. It also take into account a number of prognostic factors, such as skull base erosion, involvement of cranial nerves (47), primary tumour extension to paranasopharyngeal space (48), and the level and size of the cervical nodes (49).

In 1997, a revised AJC/UICC staging system was published (50). In this new staging system the T1 stage included tumors classified as both T1 and T2 under the old system. The new T2 stage included tumors that had extended to the nasal fossa, oropharynx, or paranasopharyngeal space. The new T3 stage covered tumors that had extended to the skull base or other paranasal sinuses. The new T4 stage covered tumors that had extended into the infratemporal fossa, orbit, hypopharynx, and cranium, or to the cranial nerves. For cervical nodal staging, N1 under the new system referred to unilateral nodal involvement, N2 bilateral nodal disease that had not reached N3 designation, irrespective of the size, number and anatomical location of the nodes. N3 referred to lymph nodes larger than 6 cm (N3a), or nodes that had extended to the supraclavicular fossa (N3b) (51). The new staging system has enabled patients to be staged more sensitively, and is a better predictor of survival (52, 53).

PROGNOSTIC FACTORS

The tumor, nodes, and metastases (TNM) staging for NPCs is the most important prognostic factor. Indeed, most other known prognostic factors are directly or indirectly related to the extent or bulk of the tumor.

A study reported in 1992 showed that the tumor's histological type and the radiotherapy dosage and coverage were also significant independent prognostic factors (54). The histological type, WHO Type I patients frequently seen among the Caucasian population were found to be associated with adverse prognosis.

Paranasopharyngeal extension was an independent prognostic factor, correlated with adverse local tumor control and increased distant spread (55) and this had been incorporated into the 1997 AJC/UICC stage system.

A large variation of tumor volume is present in T stages and primary tumor volume represents an independent prognostic factor of local control. It is more predictive with the AJC/UICC staging system than Ho's T stage classification (56). Its validity has been confirmed in patients with T3 and T4 tumors (57), and there is an estimated 1% increase in risk of local failure for every 1 cm^3 increase in primary tumor volume (58). Quantitative analysis of

circulating EBV DNA in NPC has demonstrated a positive correlation with disease stage and probably reflected the tumor load. It has been shown to have prognostic importance (59).

Analyzing the different patterns of failure, different prognostic categories can be defined across stages. T1-2N0-1 have relatively good treatment outcome; T3-4N0-1 mostly local failure; T1-2N2-3 mainly regional and distant failure and T3-4N2-3 have risk of local, regional and distant failure (60).

TREATMENT

Radiotherapy

Unlike other head and neck cancers, radiotherapy instead of surgery is the mainstay of treatment of NPC. NPC is highly radiosensitive and radiotherapy is the backbone of treatment for all stages of NPC without distant metastases.

Conventional 2 dimensional (2D) radiotherapy for NPC depends heavily on large lateral opposing fields. One of the most common radiotherapy approaches for NPC is to start phase I treatment with large lateral opposing facio-cervical fields that cover the primary tumor and the upper neck lymphatics in one volume, with matching lower anterior cervical field for lower neck lymphatics. The brainstem, spinal cord, eyes and oral cavity are protected by shieldings. When the spinal cord dose reaches 40-45 Gy, there are 2 options for phase II treatment. Treatment can either be changed to lateral opposing facial fields with anterior facial field for the primary tumor, with matching anterior cervical field for the neck lymphatics. Alternatively, treatment can be continued using the lateral opposing facio-cervical fields but with shrinkage of fields to avoid the spinal cord, and by treating the superior-posterior lymphatic with electron fields (61, 62). The major objection to treating the primary tumor and the neck lymphatic in 2 separate volumes (both of these phase II treatment techniques) is that there is a danger of underdosing the paranasopharyngeal extension of the tumor and the upper neck nodes at the junction between the primary tumor and neck lymphatic target volumes. Thus a paranasopharyngeal boost with a posterior oblique field is often employed. Radical dose of 65-75 Gy is normally given to the primary tumor and 65-70 Gy to the involved neck nodes, while the dose for prophylactic treatment for a node-negative neck is 50-60 Gy.

Conventional 2D radiotherapy successfully controlled T1 and T2 tumors in between 75% to 90% of cases, and T3 and T4 tumors in 50% to 75% of cases (63, 64). Nodal control is achieved in 90% for N0 and N1 cases, but the control rate drops to 70% for N2 and N3 cases (63). As interrupted or prolonged treatment reduces the benefits of radiotherapy, every effort should be made to maintain the treatment schedule (65).

Because of the high incidence of occult neck node involvement, prophylactic neck radiation is usually recommended (66). Good loco-regional control should be the prime objective of treatment, as loco-regional relapses represent a significant risk factor for the development of distant metastases (67).

For T1 and T2 tumors, a booster dose using intracavitary brachytherapy improved tumor control by 16% (64). Although stereotactic radiosurgery has also been used for the booster dose (68, 69), it is probably better reserved for the treatment of persistent and recurrent NPCs, because of the undesirable side effects associated with hypofractionated treatment (70).

Radiotherapy for NPC is challenging because the NP is anatomically surrounded by an array of radiosensitive structures like the brain stem, spinal cord, pituitary-hypothalamic axis, temporal lobes, eyes, middle and inner ears, and parotid glands. As NPCs tend to infiltrate and spread towards these normal organs, the irradiation target volumes in NPC are very irregular. With conventional lateral opposing fields, protection of adjacent radiosensitive organs while giving high dose to targets is difficult. Often only the critical organs like brainstem, optic pathway and spinal cord are safeguarded with adequate shieldings to avoid unacceptable radiation toxicities while non-critical organs like the parotids and auditory pathway are sacrificed during radiotherapy. For patients with early disease, since they have a good chance of survival, radiation toxicities in these even non-critical structures would affect the quality of life of survivors. However, for patients with locally advanced disease like those with skull base infiltration or intracranial extension, the challenge lies in achieving adequate tumoricidal dose to the primary without overdosing the critical organs.

The major limitations of conventional 2D radiotherapy for NPC can now be overcome with 3 dimensional (3D) conformal radiotherapy and IMRT (71, 72). IMRT is an advanced form of 3D conformal radiotherapy, conforming high dose to tumor while conforming low dose to normal tissues. 3D conformal radiotherapy employs multiple beams conforming to the shape of the target. In additional of using multiple shaped conformal beams, IMRT also allows for fine modulation of radiation intensity within each radiation beam. Thus, in effect, there are thousands of beamlets, each with calculated intensity to deposit a defined dose at each specific point. A good therapeutic ratio can be achieved by giving a high dose to the tumor to achieve high local control probability while keeping down normal tissue complications by limiting radiation dose to normal tissues. Also, IMRT planning and dose optimization is fully computerized, a process known as inverse planning, thus it is much preferred over the more expertise dependent forward planning in 3D conformal radiotherapy.

The use of IMRT in treatment of NPC have multiple advantages. Firstly, IMRT can be used for organ preservation, e. g. sparing the parotids of high dose radiation will preserve salivary function after radiotherapy; Secondly, in the case of extensive tumors, and when the tumor extension was close to the dose-limiting organs, IMRT can achieve good dose differential between the tumor and the dose-limiting organs (73, 74), and thus can achieve high dose in tumor without overdosing the normal organs. This also opens up a therapeutic window for dose escalation in

the tumor to improve local control. Thirdly, IMRT allows differential doses to be given to different targets/organs simultaneously, thus different targets/organs can receive different fractional dose at the same fraction of treatment. As the fractional dose will affect the biological effectiveness of radiation (75), there is a component of biological modulation of radiation besides just modulating the physical radiation dose in IMRT. Simultaneous modulated accelerated radiotherapy (SMART) employs this principle for accelerated radiotherapy with IMRT (76). Fourthly, IMRT resolves the problem of dose uncertainty at the junction between the primary tumor and neck lymphatic target volumes in conventional radiotherapy. It enables the primary tumor and the upper neck nodes to be treated in one volume throughout. For the above reasons, IMRT also eliminates the need of boost and hyperfractionation. Radiotherapy course can be shortened and is more efficient.

Different series reported excellent local control of more than 90% in NPC achieved with IMRT (77-81), even among patients with advanced T3-4 diseases (82). Reports also shown preservation of salivary function and improve quality of life of survivors after IMRT (83-85). A recent multicentre study also showed that the excellent 90% local control rate with IMRT as reported from single institutions are reproducible in multi-institutional setting (86). Thus, IMRT has gradually evolved as the new standard of care for NPC.

Chemotherapy

While modern radiotherapy like IMRT achieves good local control, distant metastases become the predominant pattern of failure, especially among those with loco-regionally advanced disease. NPC is also chemosensitive. There is a long history of clinical studies investigating combined radiotherapy (RT) and chemotherapy for NPC. Most of the early studies were non-randomized and the results are conflicting or inconclusive (87-96). Up to the year 1998, there were only 5 reported randomized trials on combined chemotherapy and RT for NPC (87, 90, 92, 95, 96). Each trial used a different approach with respect to drug combination, time sequence of chemotherapy and RT, and RT technique and dose. In the early randomized trials, induction chemotherapy is the most often studied combination (90, 92, 96). The rationale for induction chemotherapy is to reduce tumor load of loco-regional disease before start of RT and also early use of systemic treatment for eradication of micro-metastases. The only induction trial that showed a significant improvement of disease-free survival was the International Nasopharyngeal Carcinoma Study Group (92), using combination of bleomycin, epirubicin and cisplatin. However, there was no improvement in overall survival. This discrepancy in findings for disease-free and overall survival may be due to the increased treatment-related death among patients on induction chemotherapy which would offset the benefit of chemotherapy in reducing disease-related death.

A pivotal study was reported by the Head and Neck Intergroup in 1998, using concurrent RT with cisplatin (100 mg/sqm D1, 22, 43) followed by adjuvant cisplatin and 5-fluouracil (5-FU) (cisplatin 80 mg/sqm D1 and 5-FU 1,000 mg/sqm /D, D1-4, Q4 weeks cycles for 3 cycles) (95). Compared with RT alone, chemoradiation significantly improved progression free survival and overall survival. The pattern of disease failure showed reduction of both loco-regional and distant failure with chemoradiation.

There was initial skepticism of the Intergroup results and doubts if the results were applicable to NPC in the endemic areas. After report of the Intergroup 0099 Study, randomized trials using similar design were performed in endemic regions in Asia, to validate the Intergroup results. Three randomized trials were subsequently reported from Hong Kong (97), Singapore (98), and China (99) respectively. The study from HK used the same chemotherapy regime as the Intergroup study and showed improved failure-free survival mainly due to improved local control with chemoradiation. However, distant control and overall survival showed no significant difference (97). On the other hand, the Singapore and China studies both used a variation of dosing of cisplatin from the Intergroup regime, employing lower dose of cisplatin but given more frequently. The Singapore and Guangzhou trials both showed significant reduction of distant metastases and improvement of both disease-free and overall survival with chemoradiation (98, 99).

The meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC) study of the MAC-NPC Collaborative Group is the only meta-analysis that used an individual patient data design (100). As reported in 2006, the MAC-NPC study included 8 randomized trials which had completed accrual before end of 2001 and thus excluded the more recent trials from Asia. In the meta-analysis, there were 4 trials that investigate induction chemotherapy (+ adjuvant chemotherapy in 1 trial), 3 trials that investigate concurrent chemoradiotherapy (+ adjuvant chemotherapy in 2 trials) and 1 trial that investigate adjuvant chemotherapy alone. Overall, an absolute survival benefit of 6% at 5 yr from addition of chemotherapy was observed (from 56% to 62%). A significant interaction was observed between the timing of chemotherapy and overall survival, with the highest benefit resulting from concurrent chemoradiation. The results concur with findings from meta-analysis on other head and neck cancers also.

There is now general agreement that the positive results reported in the Intergroup 0099 study are applicable to the NPC in the endemic areas, but the conflicting evidence of chemotherapy on local control and distant metastases have generated discussion. The conclusion seems to be that, of the three basic approaches tested in these studies (induction, concurrent, and adjuvant chemotherapy), concurrent chemoradiotherapy is the most efficacious. There were 3 randomized trials that evaluated adjuvant chemotherapy and all were negative (87, 101, 102). Thus, there is still debate on whether the adjuvant chemotherapy in the Intergroup regime can be omitted.

SEQUELAE OF THERAPY

Survivors of NPC following radiotherapy or chemoradiation have impaired health-related quality of life (103, 104). Patients may suffer from a variety of late complications, many of which result from the effects of radiation on the dose-limiting organs situated adjacent to the nasopharynx and cervical lymph node. The use of chemotherapy in more advanced cases adds to the side effects, which include ototoxicity associated with cisplatin. A small proportion of the long-term sequelae represent the effects of unhealed residual damage by the tumor, such as residual cranial nerve palsies, and serous otitis media resulting from persistent disturbance of the Eustachian tube function.

These sequelae include auditory (105) problems, neuro-endocrine (106) disturbances and oral complications such as, dry mouth, poor oral and dental hygiene (107, 108). Radiation-induced soft tissue fibrosis (109), and even carotid artery stenosis might develop in the long term (110). The most debilitating sequelae are neurological complications and may include temporal lobe necrosis (111), and cranial nerve palsies (112) These lead to symptoms of dysphagia (113), and memory (114), cognitive (115), and neuropsychological dysfunctions (116).

A series of cases in which hypofractionated radiotherapy was used in combination with conventional 2D radiotherapy produced a 60% actuarial risk of complication and a 28% risk of neurological complications (117). Cutting down late complications of treatment should be one of the main objectives of future clinical trials. It has been demonstrated that shielding of the pituitary -hypothalamic axis in 2D planning and treatment can significantly reduce neuro-endocrine complications (118). Use of IMRT has been shown to improve salivary function (80, 84), but other benefits may require a longer follow-up period to confirm.

MANAGEMENT OF RESIDUAL OR RECURRENT DISEASE

Despite the improved results of concomitant chemoradiation in the management of nasopharyngeal carcinoma, there are still some patients who developed local or regional failure presenting as persistent or recurrent tumor. Early detection is essential for any form of salvage therapy to be successful. FDG-PET is superior to other imaging studies such as computed tomography or MRI in detecting residual or recurrent disease in the nasopharynx (119) and this can usually be confirmed with biopsy through endoscopic examination. Residual or recurrent tumor in the cervical lymph nodes after radiotherapy is however notoriously difficult to confirm, as in some lymph nodes only clusters of tumor cells are present (120). Sometimes the diagnosis was only confirmed after salvage surgery.

Aggressive salvage treatment for locally recurrent NPC is warranted, especially when the disease is confined to the nasopharynx. Survival after retreatment for more extensive disease remains poor, but is still higher than in patients receiving supportive treatment only (113). Even for patients with synchronous loco-regional failures, aggressive treatment should be considered for selected patients (121).

Disease in the neck

Following concomitant chemoradiation for nasopharyngeal carcinoma, isolated failure in the neck was much reduced and it was less than 5% (122). If cancer persists or recurs in the cervical lymph nodes as evidenced by imaging studies or clinical progression of the lymph nodes, salvage therapy is indicated. When external radiotherapy was employed as the salvage option, the overall 5-yr survival rate was 19.7% (123). Surgical salvage in the form of radical neck dissection could achieved a 5-yr tumor control rate of 66% in the neck and a 5-yr actuarial survival of 38% (124). When tumor in the neck lymph node exhibits extracapsular spread, brachytherapy should be applied to the tumor bed following radical neck dissection. With this adjuvant therapy, a similar tumor control rate has been achieved as when radical neck dissection was carried out for less extensive neck disease (125).

Disease in the nasopharynx

When the patient was detected to have residual or recurrent tumor in the nasopharynx after radiation or chemoradiation, this can be managed with a second course of external radiotherapy. This radiation dosage should be greater than the initial one and although a salvage rate of 32% has been achieved, the cumulative incidence of late post-reirradiation sequela was 24%, with treatment mortality of 1.8% (126). In view of the high incidence of complications resulting from the second course of radiation, stereotactic radiotherapy, brachytherapy and surgical resection have been employed for the salvage of small localized tumors in the nasopharynx. Stereotactic radiotherapy under these circumstances have a 72% 2-yr local tumor control rate (77). The number of patients treated with this method was small and long-term follow-up information is not available (127).

Brachytherapy

With the application of brachytherapy, the radiation dose decreases rapidly from the radiation source, enabling a high dose of irradiation to be delivered to the residual or recurrent tumor but a much smaller dose to surrounding tissue. Brachytherapy also delivers radiation at a continuous low dose rate, which gives it a further radiobiological advantage over fractionated external radiation. Intracavitary brachytherapy has been used for nasopharyngeal carcinomas (128). The radiation source was placed either in a tube or a mould before insertion into the nasopharynx. In view of the irregular contour of the nasopharynx and the uneven surface of the recurrent or residual tumor, it is difficult to apply the radiation source accurately to provide a tumoricidal dose. To circumvent this problem, interstitial radioactive

implants have been used to treat those small localized residual or recurrent tumor in the nasopharynx (129).

The most frequently employed radiation source for this purpose is the radioactive gold grains (^{198}Au). These gold grains can be implanted into the tumor in the nasopharynx either transnasally or using the split-palate approach (130). The latter approach gives the surgeon a direct view of the tumor and enables the implantation of the radioactive gold grains into the tumor precisely to give a better dosimetry of radiation. For those small tumors localized in the nasopharynx, without bone invasion, this method has provided effective salvage with minimal morbidity (131). The efficacy of the gold grain implants to treat persistent and recurrent tumors after radiotherapy was reported to give a 5-yr local tumor control rates of 87% and 63% respectively. The corresponding 5-yr disease-free survival rates were 68% and 60% respectively (132). Other treatments for management of localized disease with intracavitary brachytherapy have also been reported with success (133, 134).

Nasopharyngectomy

Surgical resection of the residual or recurrent tumor in the nasopharynx is another salvage option. It is indicated when the localized disease cannot be managed by brachytherapy either it is too extensive or it is located at a position, such as the cartilage of the Eustachian tube crus where gold grains cannot be implanted. When the tumor has extended to the paranasopharyngeal space, then surgical resection is indicated. Nasopharyngectomy in selected patients with localized disease is a good option of salvage. The nasopharynx, is located in the middle of the head and because of its awkward position, the exposure of the tumor in the nasopharynx for oncologic extirpation has been a difficult technical challenge. A number of approaches have been reported, including the anterior approach via the Le Forte I or the midfacial deglove route, an infratemporal approach from the lateral aspect (135), transpalatal, transmaxillary and transcervical approaches from the inferior aspect (136, 137), and an anterolateral approach (138). The mortalities associated with these salvage surgical procedures have been low, and as all the patients concerned had previously undergone radical radiotherapy, some patients develops trismus and palatal fistula. These morbidities lead to some degree of inconvenience but were still acceptable (139). With modification of surgical techniques, the palatal fistula rate associated with the maxillary swing approach has been marked reduced (140). As long as the residual or recurrent tumor can be removed adequately, the long-term results have been satisfactory. The 5-yr actuarial control of tumors in the nasopharynx has been reported to be around 65% and the 5-yr disease-free survival rate is around 54% (141, 142). In recent years, there were reports of removal of small recurrent tumor with the help of the endoscope (143, 144). The tumor has to be located at appropriate site in the nasopharynx before an oncologic resection can be performed for these patients and so far the number reported were small (145).

External radiotherapy

For more advanced or infiltrative tumors, a second course of external radiotherapy is required (146). A second course of external radiotherapy administered concurrently with chemotherapy has been tried; this was built on the experience gained from the use of concurrent chemoradiotherapy in primary treatment. This treatment has been reported to give a 5-yr actuarial overall survival rate of 26%, though the risk of major late toxicities was significant (147). The use of precision radiotherapy such as IMRT may improve the therapeutic ratio for local control, promising initial results have been reported (148), but distant metastases will remain a major issue for patients suffering from local relapse.

DISTANT METASTASIS

Despite the use of concurrent chemoradiotherapy, distant metastases remain the major cause of failure, and the prognosis for stage IV patients remains grim (149). The meta-analysis on head and neck cancer also showed that concurrent chemoradiation is the most effective sequence in combining chemotherapy and radiotherapy (150). However, induction chemotherapy showed significant reduction of distant failures (150). Thus, there is now revival of interest in using induction and concurrent chemotherapy in treatment of NPC. The Hong Kong NPC Study Group is currently still recruiting patients in a randomized trial NPC 0501 comparing induction and concurrent chemotherapy vs. concurrent and adjuvant chemotherapy (151). The results of this trial will shed more light on the optimal sequence of combining radiotherapy with chemotherapy.

Another approach to reduce distant failure is by adding targeted therapy to chemotherapy. In a recently closed, phase II trial (RTOG 0615) (152), bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor) was added to the concurrent and adjuvant phases of therapy. It was hoped that adding on anti-angiogenic agents to the primary treatment can sterilize distant micrometastases in primary treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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