Nasopharyngeal carcinoma

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Incidence of nasopharyngeal carcinoma has remained high in endemic regions. Diagnosing the disease in the early stages requires a high index of clinical acumen and, although most cross-sectional imaging investigations show the tumour with precision, confirmation is dependent on histology. Epstein-Barr virus (EBV)-encoded RNA signal is present in all nasopharyngeal carcinoma cells, and early diagnosis of the disease is possible through the detection of raised antibodies against EBV. The quantity of EBV DNA detected in blood indicates the stage and prognosis of the disease. Radiotherapy with concomitant chemotherapy has increased survival, and improved techniques (such as intensity-modulated radiotherapy), early detection of recurrence, and application of appropriate surgical salvage procedures have contributed to improved therapeutic results. Screening of high-risk individuals in endemic regions together with developments in gene therapy and immunotherapy might further improve outcome.

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Introduction

Nasopharyngeal carcinoma is a non-lymphomatous, squamous-cell carcinoma that occurs in the epithelial lining of the nasopharynx. This neoplasm shows varying degrees of differentiation and is frequently seen at the pharyngeal recess (Rosenmüller's fossa) posteromedial to the medial crura of the eustachian tube opening in the nasopharynx.[1]

The first report on a group of 14 patients who had this type of tumour was published in 1901.[2] A further clinical study of 79 patients was published in 1922.[3] The first comprehensive study of nasopharyngeal carcinoma was done in 1941, and described clinicopathological features in 114 patients.[4] This neoplasm is an uncommon disease in most countries, and its age-adjusted incidence for both sexes is less than one per 100 000 population.[5] However, the disease occurs with much greater frequency in southern China, northern Africa, and Alaska. The Inuits of Alaska[6] and ethnic Chinese people living in the province of Guangdong are especially prone to the disease. The reported incidence of nasopharyngeal carcinoma among men and women in Hong Kong (geographically adjacent to Guangdong province) is 20–30 per 100 000 and 15–20 per 100 000, respectively.[5] That the incidence of nasopharyngeal carcinoma remains high among Chinese people who have immigrated to southeast Asia or North America, but is lower among Chinese people born in North America than in those born in southern China, is noteworthy.[7,8] This finding suggests that genetic, ethnic, and environmental factors could have a role in the cause of the disease.

Pathology

The malignant epithelial cells of the nasopharynx are large polygonal cells with a syncytial composition. Their nuclei are round or oval with scanty chromatin and distinct nucleoli. The cells show no parakeratosis or cornification and are frequently intermingled with lymphoid cells in the nasopharynx, giving rise to the introduction of the term lymphoepithelioma.[9] Electronmicroscopy studies have established that these tumour cells are of squamous origin and that the undifferentiated carcinoma is a form of squamous-cell carcinoma.[10,11]

Epstein-Barr virus (EBV) is consistently detected in patients with nasopharyngeal carcinoma from regions of high and low incidence. EBV-encoded RNA signal has been shown, by in-situ hybridisation, to be present in nearly all tumour cells, whereas EBV-encoded RNA is absent from the adjacent normal tissue, except perhaps for a few scattered lymphoid cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbour EBV, which suggests that the infection occurs in the early phases of carcinogenesis.[12] Detection of a single form of viral DNA suggests that the tumours are clonal proliferations of a single cell that was initially infected with EBV. Specific EBV latent genes are consistently expressed in nasopharyngeal carcinomas and in early, dysplastic lesions. The corresponding latent viral proteins (latent membrane protein 1 and 2) have substantial effects on cellular gene expression and cellular growth, resulting in the highly invasive, malignant growth of the carcinoma.[13,14]

The histological classification of nasopharyngeal carcinoma proposed by WHO in 1978, categorised tumours into three groups: type I included typical keratinising squamous-cell carcinomas, similar to those

Search strategy and selection criteria

We did an extensive search of published work about nasopharyngeal carcinoma through the Pubmed/MEDLINE database from 2004 back to the mid-60's, and this search included the OLDMEDLINE. We also searched The Cochrane Library for review articles published between 1990 and 2003. Search terms included: "nasopharyngeal carcinoma", "nasopharynx cancer", "radiotherapy", "chemotherapy", "salvage therapy", "nasopharyngectomy", "combined treatment modality", "clinical trials", "randomized controlled trials", and "meta-analysis". The searches included reports of studies on human beings and were those published in English. Priority of selection was large contemporary clinical trials or studies. Abstracts of recent pertinent medical conferences were also included for information about latest developments. Most of the publications used were from work published within the past 15 years, although we have also included a few highly regarded old articles.

found in the rest of the upper aerodigestive tract; type II included non-keratinising squamous carcinomas; and type III included undifferentiated carcinomas (panel).[15] An alternative classification has divided tumours into two histological types, namely squamous-cell carcinomas and undifferentiated carcinomas of the nasopharyngeal type.[16] The second classification is correlated with EBV serology: patients with squamous-cell carcinomas have a reduced EBV titre, whereas those with undifferentiated carcinomas of the nasopharyngeal type have raised titres. In North America, around 25% of tumour patients have type I histology, 12% have type II, and 63% have type III. The histological distribution in southern Chinese patients is 2%, 3%, and 95%, respectively.[17]

Biopsies obtained from nasopharyngeal carcinomas sometimes show a mixed histological pattern, and this pattern varies among different parts of the tumour. The most recent WHO classification has taken this mixed pattern into account as well as the association of EBV with type II and type III tumours. The histological types of nasopharyngeal carcinoma are now defined either as squamous-cell carcinomas or non-keratinising carcinomas, and the second group is subdivided into differentiated and undifferentiated carcinomas.[18] This classification is more applicable for epidemiological research and has also been shown to have a prognostic bearing. Undifferentiated carcinomas have a higher local tumour control rate with treatment and a higher incidence of distant metastasis than do differentiated carcinomas.[19,20]

Symptoms and serological diagnosis

Patients with nasopharyngeal carcinoma can present with symptoms from one or more of four categories. The categories consist of (1) presence of tumour mass in the nasopharynx (epistaxis, nasal obstruction, and discharge); (2) dysfunction of the eustachian tube, associated with the lateroposterior extension of the tumour to the paranasopharyngeal space (tinnitus and deafness); (3) skull-base erosion and palsy of the fifth and sixth cranial nerves, associated with the superior extension of the tumour (headache, diplopia, facial pain and numbness); and (4) neck masses, usually appearing first in the upper neck. Symptoms such as anorexia and weight loss are uncommon in patients with nasopharyngeal carcinomas and distant spread should be suspected when such symptoms are present. Unfortunately, because of the non-specific nature of the nasal and aural symptoms and the difficulty of making a clinical examination of the nasopharynx, most patients with the disease are diagnosed only when the tumour has reached an advanced stage (stages III and IV).

A retrospective analysis of 4768 patients identified symptoms of nasopharyngeal carcinoma at presentation as neck mass (76%), nasal dysfunction (73%), aural dysfunction (62%), headache (35%), diplopia (11%), facial numbness (8%), weight loss (7%), and trismus (3%). The physical signs present at diagnosis were enlarged neck node (75%) and cranial nerve palsy (20%). The cranial nerves most commonly affected were the third, fifth, sixth, and 12th nerves.[21,22] The presenting symptoms in young patients were in general similar to those reported in adults.[23]

Patients who present with symptoms of nasopharyngeal carcinoma should be clinically assessed for physical signs of the disease. A positive EBV serology test will give further grounds for suspicion and would justify an endoscopic examination and a biopsy from the nasopharynx. If the clinical suspicion for nasopharyngeal carcinoma is high, even if the suspected tumour is not visualised with endoscopic examination, cross-sectional imaging by CT or MRI should be undertaken. A definitive diagnosis of nasopharyngeal carcinoma needs a positive biopsy taken from the tumour in the nasopharynx, supported either by its visualisation in the nasopharynx or (in the case of predominantly submucosal tumours) its visualisation with cross-sectional imaging.

Panel: WHO histological classification of nasopharyngeal carcinoma[15]

Keratinising squamous-cell carcinoma (WHO type I)
This type of nasopharyngeal carcinoma shows squamous differentiation with the presence of intercellular bridges and/or keratinisation over most of its extent.

Non-keratinising carcinoma
This group comprises a differentiated type of non-keratinising carcinoma and an undifferentiated type. These tumours are generally more radiosensitive than squamous cell carcinoma and have stronger relationships with the Epstein-Barr virus.

1. Differentiated non-keratinising carcinoma (WHO type II)
   The tumour cells show differentiation with a maturation sequence that results in cells in which squamous differentiation is not evident on light microscopy.
2. Undifferentiated carcinoma (WHO type III)
   The tumour cells have oval or round vesicular nuclei and prominent nucleoli. The cell margins are indistinct, and the tumour exhibits a syncytial rather than pavemented appearance.

Population screening

In southern China, where nasopharyngeal carcinoma is endemic, EBV serology has been used for population screening. In a study undertaken in Wuzhou (Guangxi province, China)[24] in the early 1980s, 1136 individuals identified as positive for immunoglobulin A against viral capsid antigen received regular clinical examinations of the nasopharynx and neck for 4 years. During this follow-up period, 35 cases of nasopharyngeal carcinoma were detected, most of which (92%) were diagnosed early at either stage I or stage II. The annual detection rate of nasopharyngeal carcinoma for this group was 31·7 times higher than for the population as a whole.

Similar results were reported from another study done in Zhongshan (Guangdong province, China).[25] The sensitivity and predictive value of serology in population screening was proposed to be improved by testing against a panel of EBV antibodies.[26] The predictive value of EBV serology for nasopharyngeal carcinoma was lent support by a more recent report from Taiwan.[27] In this study, the initial EBV serology of 9699 study participants was cross-checked against the cancer registry and death registry in the ensuing 15-year period. The duration of follow-up was correlated with the difference in the cumulative incidence of nasopharyngeal carcinoma between seropositive and seronegative patients. Prospective studies are now needed to assess the effect of such population-based screening, in terms of the reduction in mortality related to nasopharyngeal carcinoma in the screened population; the risk-benefit ratio (risks from endoscopic examination and biopsies); and cost-effectiveness.

Imaging studies

Before the introduction of cross-sectional imaging, little was known about the natural behaviour and routes of extension of nasopharyngeal carcinomas in the early stages of development. Surgery was not a primary treatment, and post-mortem examinations of patients who died from nasopharyngeal carcinoma were of little importance since the tumours were usually very advanced by the time of death and had undergone significant secondary changes as a result of treatment. The best that could be done was to use plain radiographs to assess bone destruction and soft tissue mass abutting on the upper airway, but these techniques were of low sensitivity and specificity and added little to our knowledge of invasion and extension of the disease.

Clinical examination (including endoscopic examination) can provide valuable information about mucosal involvement and tumour extension into the nasal fossae and oropharynx, but cannot ascertain deep extension, skull-base erosion, or intracranial spread, except where there are tell-tale symptoms and signs of gross extension along these routes. Cross-sectional imaging has revolutionised and improved the effectiveness of treatment for nasopharyngeal carcinoma. In terms of contribution to staging, CT has identified paranasopharyngeal extension as one of the most common modes of extension of nasopharyngeal carcinoma[28] and has shown perineural spread through the foramen ovale to be 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.[29]

MRI is better than CT for displaying both superficial and deep nasopharyngeal soft tissue and for differentiating tumour from soft tissue. MRI is also more sensitive for assessment of retropharyngeal and deep cervical nodal metastases.[30] However, the technique is of limited effectiveness for assessing bone details and CT should be undertaken when the status of the base of the skull cannot be satisfactorily established with MRI.[31] In terms of staging, MRI is able to detect marrow infiltration by tumours, whereas CT cannot detect this kind of infiltration unless there is associated bone erosion. This kind of marrow infiltration has been suggested to be associated with an increased risk of distant metastases.[32]

Detection of distant metastases at diagnosis with conventional radiographs, CT, and MRI is not usually successful. Several reports have concluded that bone scans,[33] liver scintigraphy,[34] abdominal ultrasonography,[35] and marrow biopsy[36] are of little value in routine staging and have recommended that they need not be used. A study concluded that there was no evidence to lend support to distant imaging for low-risk (N0 or stage I) disease, but recommended that high-risk (N3) disease should be fully staged with chest radiography, bone scan, and liver ultrasonography.[37] The role of positron emission tomography (PET) in the detection of distant metastases in other malignancies has been established,[38] but its application in the staging of nasopharyngeal carcinoma has not been ascertained.

Cross-sectional imaging displays the extent of the primary tumour with unprecedented precision. This accuracy enables radiotherapy treatment to be designed and administered more accurately, effectively improving the outcomes for this form of treatment.[39] Even better results have become possible with intensity modulated radiotherapy, which makes use of composite CT-MRI targets[40] enabling radiotherapy to be targeted even more accurately onto tumours, sparing adjacent tissues.

When used to monitor a patient's condition after treatment, both CT and MRI have low sensitivity and moderate specificity in the detection of tumour recurrence;[41] although, in general, MRI is better than CT in showing tumour recurrence and postradiation complications.[42] Recurrent nasopharyngeal carcinomas can exhibit a variety of signal intensities and contours, and these can be difficult to interpret.[43] However, CT can show bone regeneration after treatment, which could be an indication of the complete eradication of the tumour in the affected area[44] suggesting a favourable prognosis with related clinical findings.[45] PET has been reported to be more sensitive than CT and MRI at detecting residual and recurrent tumours in the nasopharynx.[46]

Staging system

There are various ways of classifying nasopharyngeal carcinomas. At present the American Joint Committee on Cancer Staging and End Result Reporting/ International Union Against Cancer (AJC/UICC) system is preferred in Europe and America,[47] whereas Ho's system is frequently used in Asia.[48,49] The nodal classification in Ho's system has incorporated prognostic significance, but the stratification of the

T stages into five sectors differs from most staging systems.

The development of a revised staging system in the past decade was motivated by the desire to incorporate experiences gained from various centres around the world, taking into account many prognostic factors, including skull-base erosion, involvement of cranial nerves,[50] primary tumour extension to paranasopharyngeal space,[51] and the level and size of the cervical nodes.[52] A revised AJC/UICC staging system was published in 1997;[53] in this new staging system the T1 stage included tumours classified as both T1 and T2 under the old system. The new T2 stage covered tumours that had extended to the nasal fossa, oropharynx, or paranasopharyngeal space. The new T3 stage covered tumours that had extended to the skull base or other paranasal sinuses. The new T4 stage covered tumours 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 to bilateral nodal disease that had not reached N3 designation, irrespective of the size, number, and anatomical location of the nodes; and N3 to lymph nodes larger than 6cm (N3a), or nodes that had extended to the supraclavicular fossa (N3b).[54] The new staging system has enabled patients to be staged more sensitively and is a better predictor of survival than the old system (table 1).[55,56]

Prognosis

As with most other tumours, the extent of a nasopharyngeal carcinoma as embodied in the TMN staging system (table 1) is the most important prognostic factor. Indeed, most other known prognostic factors are directly or indirectly related to the extent or bulk of the tumour. The changes in prognostic factors identified and reported at different times in the past probably represented adoption of these known adverse factors in the new staging systems, or the use of treatment strategies to address these known adverse prognostic factors and to nullify their adverse effects.

A report in 1990[57] showed that, besides the T and N stages, other prognostic factors included size and degree of fixation of neck nodes, sex, age, the presence of cranial nerve palsy, and ear symptoms at presentation. The factors of size of lymph node and ear symptoms probably suggest the lack of recognition of nodal size and paranasopharyngeal extension in the T and N staging system used at that time. A study reported in 1992[58] showed that the tumour's histological type and the radiotherapy dose and coverage were also significant independent prognostic factors. The adverse prognostic factor of histological type is shown in this report, which included mainly the white population with WHO type I histology. Paranasopharyngeal extension was an independent prognostic factor correlated with adverse local tumour control and increased distant spread.[59] Even after paranasopharyngeal extension of tumour had been incorporated into the 1997 AJC/UICC stage classifications, the adverse prognostic effect remains valid despite the use of concurrent chemoradiotherapy.[60]

A large variation of tumour volume is present in T stages of different staging systems, and primary tumour volume represents an independent prognostic factor of local control and is more predictive with the AJC/UICC staging system than with Ho's T stage classification.[61] Validity of tumour volume has been confirmed in patients with T3 and T4 tumours,[62] and there is an estimated 1% increase in risk of local failure for every 1 cm^3 increase in primary tumour volume.[63] In addition to direct measurement of tumour volume, quantitative analysis of circulating EBV DNA in nasopharyngeal carcinoma has shown a positive correlation with disease stage and a strong relation with clinical events, as well as exhibiting prognostic importance.[64]

Based on the difference in failure patterns, different prognostic categories can be defined across stages. These are (1) T1–2N0–1 (relatively good treatment outcome); (2) T3–4N0–1 (mainly local failure); (3) T1–2N2–3 (mainly regional and distant failure); and (4) T3–4N2–3 (local, regional and distant failure). These prognostic groupings will have important implications for the selection of appropriate treatment strategies and the design of future clinical trials to address different failure patterns.[65] There is early evidence that for advanced diseases, adding chemotherapy to radiotherapy will improve treatment outcome, both in terms of locoregional control and distant metastases.[66,67]

Treatment

Radiotherapy

Radiotherapy is the standard treatment for nasopharyngeal carcinoma. Unfortunately, it can produce undesirable complications after treatment because of the location of the tumour at the base of skull, closely surrounded by and in close proximity to radiation dose-limiting organs, including the brain stem, spinal cord, pituitary-hypothalamic axis, temporal lobes, eyes, middle and inner ears, and parotid glands. Since nasopharyngeal carcinomas tend to infiltrate and spread towards these dose-limiting organs, they are even more difficult to protect.

One of the most common radiotherapy approaches for nasopharyngeal carcinoma is to start phase I treatment with large lateral opposing faciocervical fields that cover the primary tumour and the upper neck lymphatics in one volume, with matching lower anterior cervical field for lower neck lymphatics. When the spinal cord dose reaches 40–45 Gy, there are two options for phase II treatment. Treatment can either be changed to lateral opposing facial fields with anterior facial field for the primary tumour, with matching anterior cervical field

for the neck lymphatics. Alternatively, treatment can be continued with the lateral opposing faciocervical fields but with shrinkage of fields to avoid the spinal cord, and by treating the superior-posterior lymphatic with electron fields.[68,69] The major objection to treating the primary tumour and the neck lymphatic in two separate volumes (both of these phase II treatment techniques) is that there is a danger of underdosing the paranasopharyngeal extension of the tumour and the upper neck nodes at the junction between the primary tumour and neck lymphatic target volumes.

In radiotherapy a dose of 65–75 Gy is normally given to the primary tumour and 65–70 Gy to the involved neck nodes, whereas the dose for prophylactic treatment for a node-negative neck is 50–60 Gy. This treatment has successfully controlled T1 and T2 tumours in 75–90% of cases and T3 and T4 tumours in 50–75% of cases.[65,68–71] Nodal control is achieved in 90% of N0 and N1 cases, but the control rate drops to 70% for N2 and N3 cases.[65] As interrupted or prolonged treatment reduces the benefits of radiotherapy, every effort should be made to maintain the treatment schedule.[72] Because of the high incidence

The American Joint Committee on Cancer Staging[53]				Ho Staging[49]		
Tumour in nasopharynx (T)				**Primary tumour (T)**		
T1	Tumour confined to the nasopharynx			T1	Tumour confined to nasopharynx (space behind choanal orifices and nasal septum and above posterior margin of soft palate in resting position)	
T2	Tumour extends to soft tissues of oropharynx and/or nasal fossa			T2	Tumour extended to nasal fossa, oropharynx, or adjacent muscles or nerves below base of skull	
T2a	without parapharyngeal extension					
T2b	with parapharyngeal extension					
T3	Tumour invades bony structures and/or paranasal sinuses			T3	Tumour extended beyond T2 limits and subclassified as follows:	
				T3a	Bone involvement below base of skull (floor of sphenoid sinus is included in this category)	
				T3b	Involvement of base of skull	
				T3c	Involvement of cranial nerve(s)	
				T3d	Involvement of orbits, laryngopharynx (hypopharynx), or infratemporal fossa	
T4	Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit					
Regional lymph nodes (N)				**Regional lymph nodes (N)**		
The distribution and the prognostic effect of regional lymph node spread from nasopharynx cancer, especially of the undifferentiated type, is different from that of other head and neck mucosal cancers and justifies use of a different N classification scheme.						
NX	Regional lymph nodes cannot be assessed					
N0	No regional lymph node metastasis			N0	Node palpable or thought to be benign	
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa			N1	Node(s) wholly in upper cervical level, bounded below by the skin crease extending laterally and backward from or just below thyroid notch (laryngeal eminence)	
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa			N2	Node(s) palpable between crease and supraclavicular fossa, the upper limit being a line joining the upper margin of the sternal end of the clavicle and the angle formed by the lateral surface of the neck and the superior margin of the trapezius	
N3	Metastasis in a lymph node(s)			N3	Node(s) palpable in the supraclavicular fossa and/or skin involvement in the form of carcinoma en cuirasse or satellite nodules above the clavicles	
N3a	greater than 6 cm in dimension					
N3b	extension to the supraclavicular fossa					
Distant metastasis (M)				**Metastases (M)**		
MX	Distant metastasis cannot be assessed					
M0	No distant metastasis			M0	No haematogenous metastases	
M1	Distant metastasis			M1	Haematogenous metastases present, and/or lymph nodal metastases below the clavicle	
Stage grouping				**Stage grouping**		
Stage 0	T1s	N0	M0			
Stage I	T1	N0	M0	Stage I	T1,	N0
Stage IIA	T2a	N0	M0	Stage II	T2 and/or N1	
Stage IIB	T1	N1	M0			
	T2	N1	M0			
	T2a	N1	M0			
	T2b	N0	M0			
	T2b	N1	M0			
Stage III	T1	N2	M0	Stage III	T3 and/or N2	
	T2a	N2	M0			
	T2b	N2	M0			
	T3	N0	M0			
	T3	N1	M0			
	T3	N2	M0			
Stage IVA	T4	N0	M0	Stage IV	N3 (any T)	
	T4	N1	M0			
	T4	N2	M0			
Stage IVB	Any T	N3	M0			
Stage IVC	Any T	Any N	M1			
				Stage V	M1	

Table 1: **Staging systems for nasopharyngeal carcinoma**

of occult neck node involvement, prophylactic neck radiation is usually recommended.[73] Good locoregional control should be the prime objective of treatment since locoregional relapses represent a significant risk factor for the development of distant metastases.[74] For T1 and T2 tumours, a booster dose by use of intracavitary brachytherapy improved tumour control by 16%.[75] Although stereotactic radiosurgery has also been used for the booster dose,[76] it is probably better reserved for the treatment of persistent and recurrent nasopharyngeal carcinomas because of the undesirable side-effects associated with hypofractionated treatment.[77]

The major limitations of 2D planning for nasopharyngeal carcinoma can now be overcome with 3D conformal radiotherapy and intensity-modulated radiotherapy.[78,79] When applied alone, 3D conformal boost is not effective,[80] thus conformal radiotherapy and intensity-modulated radiotherapy should be adopted throughout the treatment. In the case of extensive tumours, and when the tumour extension is close to the dose-limiting organs, intensity-modulated radiotherapy is distinctly preferable to 3D conformal planning because it further improves the dose differential between the tumour and the dose-limiting organs.[81,82] Intensity-modulated radiotherapy also resolves the problem of dose uncertainty at the junction between the primary tumour and neck lymphatic target volumes as it enables the primary tumour and the upper neck nodes to be treated in one volume throughout. Although this technique theoretically allows very good dose differential between the tumour and the sensitive adjacent normal tissue structures, the optimum safety margin needed between gross tumour and adjacent tissues has still not been established. Until this dose differential information is available, the clinical target volume of the primary tumour should be defined cautiously in planning. Randomised prospective trials should enable the clinical target volume to be more accurately defined.

Intensity-modulated radiotherapy has achieved excellent locoregional control of nasopharyngeal carcinomas.[83] A study that prospectively assessed salivary functions confirmed the gradual recovery of parotid function within 2 years after completion of intensity-modulated radiotherapy.[84] Satisfactory dosimetric results were also achieved with this treatment for recurrent nasopharyngeal carcinomas, and the degree of short-term control was encouraging.[85] Other attempts to enhance the biological effects of radiotherapy have been reported. These attempts include accelerated fractionation,[86] accelerated hyperfractionation,[87] and a combination of one or other of these treatments with chemotherapy.[88,89] However, hyperfractionation radiotherapy for nasopharyngeal carcinoma should be used with care, because a study of accelerated hyperfractionation by 2D radiotherapy planning has reported an increase in radiation damage to the CNS without improvement in tumour control.[90]

Chemotherapy

Several studies in the past two decades have reported the results of the use of chemotherapy in combination with radiotherapy for the management of locoregional advanced cases of nasopharyngeal carcinoma. Twelve randomised controlled trials have reported on neoadjuvant, concurrent, and adjuvant therapy, or on a combination of these approaches. Nine of these studies were reported before 2004 and included four neoadjuvant chemotherapy studies,[91–94] three concurrent chemotherapy studies,[66,67,95] and two adjuvant studies.[96,97] One of the concurrent studies[95] has recently been updated,[98] and two of the neoadjuvant studies[92,93] have been updated and pooled for meta-analysis.[99] Three more concurrent chemotherapy studies have been reported from Hong Kong and Singapore.[100–102] Results differed between studies that used neoadjuvant, those that used concurrent, and those that used adjuvant chemotherapy in combination with radiotherapy. In addition to the difference in chemotherapy schedules, the effect of staging classification and of stage migration for studies reported at different times could explain these reported differences in results (table 2).

The Intergroup 1997 study[66] was the first study to show that use of chemotherapy alongside radiotherapy improved overall survival compared with radiotherapy alone. Because this study included cases of well-differentiated carcinomas, there were initial doubts as to whether the results were applicable to nasopharyngeal carcinoma in endemic areas. However, a subsequent report from Taiwan[67] lent support to the benefits of this approach. In fact, these studies were the only two to show an improvement in both relapse-free survival and overall survival.

As far as the other concurrent studies were concerned, one study[102] reported an improvement in overall survival, and another study[100] reported a borderline improvement in overall survival. However, neither study showed any evidence of improved relapse-free survival, and the disparity between overall survival and relapse-free survival was apparently explained by improvement in control of distant metastases in the absence of improved locoregional control. The updated concurrent study[98] also reported an improvement in overall survival but no improvement in relapse-free survival. A further study[101] reported an improvement in actuarial loco-regional control at 3 years, but no improvement in relapse-free survival or overall survival, and a significant increase in ototoxicity in the treatment group. The long-term follow-up reports from these more recent studies are expected to provide more definitive results than at present.

Two of the four neoadjuvant studies[91,93] reported improvement in relapse-free survival but no improvement in overall survival. The others[92,94] reported no improvement generally. A meta-analysis[99] noted improvements in relapse-free survival and disease-specific survival. However, overall survival was not

improved because of the increase in intercurrent deaths in the treatment group. Promising results have also been reported from phase II studies of advanced nasopharyngeal carcinoma treated with alternating weekly chemotherapy with cisplatin and 5-fluorouracil/folinic acid.[103] The two adjuvant chemotherapy studies[96,97] reported no improvement either in relapse-free survival or overall survival.

Studies trying to improve on the use of concurrent chemotherapy plus adjuvant chemotherapy have been reported with objectives varying from improvement of tolerance and side-effects to improvement of efficacy for the more advanced cases. The poor compliance with adjuvant chemotherapy after concurrent chemoradiotherapy can be overcome by the use of neoadjuvant chemotherapy. A study on neoadjuvant chemotherapy followed by concomitant chemoradiotherapy has reported excellent overall survival and acceptable toxicity.[104] Replacement of cisplatin with other chemotherapeutic agents in part of the treatment could overcome or reduce the ototoxicity associated with six courses of cisplatin. A study using cisplatin concurrently with radiotherapy, followed by adjuvant ifosfamide, 5-fluorouracil, and leucovorin, for patients with stage IVb nasopharyngeal carcinoma has been reported.[105] Although the patients concerned had disease at a more advanced stage, the outcomes of this group were comparable with those reported in other series of patients with less advanced disease for whom platinum-based adjuvant chemotherapy was used. The chemotherapy regime also has an acceptable compliance rate.

Although the stage I and II cases were generally considered to have resulted in relatively good treatment outcomes, analysis has shown that the American Joint Committee on Cancer Screening 1997 system has allowed more patients with a poor prognosis to be grouped under stage II.[106] With such stage migration of the more advanced cases to stage II, and early evidence that disease-free survival is much the same for stage II patients with a raised tumour burden after treatment with concurrent chemoradiotherapy and for stage I patients treated with radiotherapy alone, the role of concurrent chemoradiotherapy should be explored for stage II patients.[107] An international effort is now underway to undertake a meta-analysis of updated data from many of these reported randomised controlled trials, with more than 1700 patients. The results of this meta-analysis are eagerly awaited.

There is now general agreement that the positive results reported in the Intergroup 1997 study[66] are applicable to nasopharyngeal carcinoma in 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 (neoadjuvant, concurrent, and adjuvant chemotherapy), concurrent chemoradiotherapy is the most efficacious. Nevertheless, the classic principles of chemoradiotherapy timing (namely, that concurrent chemoradiotherapy provides more effective local control, whereas sequential use of chemotherapy and radiotherapy is more effective with distant metastases) have not been borne out by the study results.[108] Despite the use of concurrent chemoradiotherapy, distant metastases remain the major cause of treatment failure,[32] and the outlook for stage IV patients remains poor.[109]

Follow-up

Clinical

Documentation of complete remission in the nasopharynx and neck lymphatics, with the application of clinical examination, endoscopic examination with or without biopsy, and imaging studies, is important. For assessment of complete remission in the nasopharynx, the decision about where to draw the line between a slow regressing tumour and a residual tumour remains

	Number of patients	Timing of chemotherapy	% disease-free survival (years)		% overall survival (years)	
			RT	RT/CT	RT	RT/CT
Institute Nationale Tumori, Italy[94]	229	Adjuvant: vincristine, doxorubicin, cyclophosphamide ×6 cycles	56 (4)	58 (4)	67 (4)	59 (4)
International NPC Study Group[89]	339	Neoadjuvant: bleomycin, epirubicin, cisplatin ×3 cycles	30 (5)*	39 (5)*	46 (5)	40 (5)
Intergroup 0099[64]	147	Concurrent: cisplatin ×3 cycles, then adjuvant: cisplatin, 5-FU for 3 cycles	24 (3)*	69 (3)*	47 (3)*	78 (3)*
Asian Oceanian Clinical Oncology Association[90]	334	Neoadjuvant: epirubicin, cisplatin ×2–3 cycles	42 (3)	48 (3)	71 (3)	78 (3)
Sun Yat-sen University, Guangzhou[91]	456	Neoadjuvant: bleomycin, cisplatin, 5-FU ×2–3 cycles	49 (5)*	59 (5)*	56 (5)	63 (5)
Sun Yat-sen University, Guangzhou + Asian Oceanian Clinical Oncology Association (pooled updated)[97]	784	Neoadjuvant: bleomycin, cisplatin, 5-FU ×2–3 cycles OR Neoadjuvant: epirubicin, cisplatin ×2–3 cycles	43 (5)*	51 (5)*	58 (5)*†	64 (5)*†
Prince of Wales Hospital, Hong Kong[93]	350	Concurrent: cisplatin ×8 cycles weekly	69 (2)	76 (2)		
Prince of Wales Hospital, Hong Kong (updated)[96]	350	Concurrent: cisplatin ×8 cycles weekly	52 (5)	62 (5)	59 (5)*	72 (5)*
Sapporo Medical University, Japan[92]	80	Neoadjuvant: cisplatin, 5-FU ×2 cycles	43 (5)	55 (5)	48 (5)	60 (5)
National Yang-Ming University, Taiwan[95]	157	Adjuvant: cisplatin, 5-FU ×9 cycles weekly	50 (5)	54 (5)	61 (5)	55 (5)
Taichung Veterans General Hospital, Taiwan[101]	284	Concurrent: cisplatin, 5-FU for 2 cycles	53 (5)*	72 (5)*	54 (5)*	72 (5)*
Queen Mary Hospital, Hong Kong[98]	219	Concurrent: uracil, then adjuvant: cisplatin, 5-FU alternating with vincristine, bleomycin, methotrexate ×6 cycles overall	58 (3)	69 (3)	77 (3)‡	87 (3)‡
National Cancer Centre, Singapore[100]	220	Concurrent: cisplatin ×3 cycles, then adjuvant cisplatin, 5-FU for 3 cycles	62 (2)	76 (2)	77 (2)*	85 (2)*
Hong Kong NPC Study Group[99]	348	Concurrent: cisplatin ×3 cycles, then adjuvant: cisplatin, 5-FU for 3 cycles	61 (3)	69 (3)	79 (3)	78 (3)

* $p<0.05$; †disease-specific survival; ‡$p=0.06$; RT=radiotherapy alone; RT/CT=combined radiotherapy and chemotherapy arm; 5FU=5-fluorouracil.

***Table 2*: Results of randomised prospective studies on application of chemotherapy and radiotherapy in the management of nasopharyngeal carcinoma**

problematic, but in most cases salvage treatment should not be delayed for longer than about 10 weeks.[110] Residual tumours in the nasopharynx can be treated with either cone down fields[111] or brachytherapy[112] with good results, and residual neck node disease is amenable to radical neck dissection.

Clinical and imaging follow-up of patients is recommended because locoregional relapses, if detected early, are amenable to radical salvage treatment.[113] The recommended follow-up procedures include clinical examination of the nasopharynx (including an endoscopic examination) and neck, and regular imaging every 4–6 months during the initial 3–5 years after treatment.[114,115] Endoscopic examination should be used to detect superficial tumours, and cross-section imaging should be used to detect deep infiltrating tumours not associated with mucosal lesion.[31] An imaging study comparing PET with MRI for detection of residual and recurrent tumour has reported PET as the superior modality.[46] For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options.[116]

EBV gene

Circulating free EBV DNA has been reported in patients with nasopharyngeal carcinoma,[117] and the increased number of copies of EBV DNA in the blood during the initial phase of radiotherapy suggests that the viral DNA was released into the circulation after cell death.[118] The quantity of free plasma EBV DNA, as measured by real-time quantitative PCR, is related to the stage of the disease. The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival.[119] A study has reported that the levels of post-treatment EBV DNA compared with pretreatment EBV DNA are a good predictor of progression-free survival.[120] When EBV DNA was used together with immunoglobulin A against the viral capsid antigen of EBV, the sensitivity of early diagnosis of nasopharyngeal carcinoma increased.[121] Raised levels of EBV DNA were only detected in 67% of patients with locoregional recurrence,[116,122] although in those with distant metastasis levels of EBV DNA copies were heightened before the appearance of clinical abnormality.[116]

Sequelae of therapy

Survivors of nasopharyngeal carcinoma have impaired health-related quality of life.[123,124] Patients who survive the disease can have several late complications, many of which result from the effects of radiation on the dose-limiting organs adjacent to the nasopharynx and neck nodes. The use of chemotherapy in more advanced cases adds to the side-effects, which include ototoxicity associated with cisplatin.[100] A small proportion of the long-term sequelae represent the effects of unhealed residual damage by the tumour, such as residual cranial nerve palsies and serous otitis media resulting from persistent disturbance of the eustachian-tube function. These sequelae include neuro-endocrine[125] and auditory[126] complications, dry mouth, poor oral and dental hygiene,[127,128] radiation-induced soft tissue fibrosis,[129] and carotid artery stenosis.[130] The most debilitating sequelae are neurological complications. These can include serious disorders such as temporal lobe necrosis,[131] cranial nerve palsies[132] and dysphagia,[133] and also less obvious effects such as memory loss,[134] cognitive dysfunction,[135] and neuropsychological dysfunction[136] (table 3).

A series of cases in which hypofractionated radiotherapy was used in combination with 2D planning produced a 60% actuarial risk of complication and a 28% risk of neurological complications.[137] Cutting down late complications of treatment should be one of the main objectives of future clinical trials. Shielding of the pituitary-hypothalamic axis in 2D planning and treatment has been shown to significantly reduce neuroendocrine complications.[138] Use of intensity-modulated radiotherapy has been shown to improve salivary function,[84] but other benefits need a longer follow-up period to confirm.

	Time of assessment	Risk and details of sequelae
Side-effects associated with hypofractionated radiotherapy[135]	10 years	31% of patients developed one or more late irradiation sequelae. Most were mild soft-tissue damages. Neurological damage that occurred in 10% of patients constituted the major morbidity and accounted for most of the treatment mortalities (1%)
Hypothalamic-pituitary function[123]	5 years	With life table analysis, the cumulative probability of endocrine dysfunction was estimated to be 62% after 5 years. These include disturbances of growth hormone, gonadotropins, corticotropin, and/or thyrotropin. The progressive impairment in hypothalamic pituitary function leading to endocrine dysfunction that requires treatment occurs in 50% of patients at 5 years after cranial irradiation
Long-term sensorineural hearing deficit[124]	2 years	Within 3 months after radiotherapy, deterioration of bone conduction threshold at 4 kHz was noted in 31% of ears. In 40% of these ears, recovery was evident at 2 years
Dental and oral hygiene[127]	1–4 years	Xerostomia (92%), trismus (29%), higher prevalence of clinical candidosis (24%)
Carotid artery stenosis[128]	>5 years	15 times increase in risk of developing significant carotid stenosis
Temporal lobe necrosis[129]	5 years	5-year actuarial incidence ranged from 0% to 14% (dependent on fractional and total dose)
Cranial nerve palsy[130]	1–20 years	Hypoglossal palsy, vagus palsy, recurrent laryngeal nerve palsy, and accessory palsies. Often associated with marked neck fibrosis
Dysphagia[131]	Not stated	Swallowing function continues to deteriorate over time, even many years after radiation therapy
Memory loss[132]	>2 years	Visual memory performance deteriorated with time, while verbal memory remained more stable
Cognitive function associated with temporal lobe necrosis[133]	>1 year	For patients who developed temporal lobe necrosis after radiotherapy, memory, language, motor ability, and executive functions were significantly impaired, although their general intelligence remained relatively intact

Table 3: **Late complications of radiotherapy for the treatment of nasopharyngeal carcinoma**

Management of residual or recurrent disease

Despite the effectiveness of radiation and chemotherapy in the management of nasopharyngeal carcinoma, local failure or regional failure presenting as persistent or recurrent tumour still occurs. To attain a high salvage rate, early detection and treatment is essential.[18] FDG-PET is better than CT in detecting residual or recurrent disease in the nasopharynx,[139] and its results can usually be confirmed with biopsy through endoscopic examination. Residual or recurrent tumour in the neck after radiotherapy is notoriously difficult to confirm because in some lymph nodes only clusters of tumour cells are present.[140] Aggressive treatment for locally recurrent nasopharyngeal carcinoma is warranted, especially in cases where 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 locoregional failures, aggressive treatment should be considered for selected patients[141] (table 4).

Disease in the neck

After combined chemoradiation for nasopharyngeal carcinoma, isolated failure in the neck is less than 5%.[146] 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 needed. When managed with another course of external radiotherapy, the overall 5-year survival rate is around 20%.[147] Radical neck dissection as a form of surgical salvage has achieved a 5-year tumour control rate of 66% in the neck and a 5-year actuarial survival of 38%.[142] When tumour in the neck node extends beyond the confines of the lymph node, brachytherapy should be applied to the tumour bed in addition to radical neck dissection. With this adjuvant therapy, a similar tumour control rate has been achieved as for radical neck dissection for less extensive neck disease.[148]

Disease in the nasopharynx

Residual or recurrent disease in the nasopharynx can be managed with a second course of external radiotherapy. The dosage should be greater than the initial radiation dose. Although a salvage rate of 32% has been achieved, the cumulative incidence of late sequelae after re-irradiation is 24% with treatment mortality of 1·8%.[149] To avoid the high incidence of complications resulting from re-irradiation, stereotactic radiotherapy, brachytherapy, and surgical resection have been used for patients with small localised tumours in the nasopharynx. Stereotactic radiotherapy, when used for the management of residual or recurrent tumour, is associated with a 2-year local tumour control rate of 72%.[77] However, only a few patients have been treated with this method, and long-term follow-up information is not available.[150]

Brachytherapy

With brachytherapy, the radiation dose decreases rapidly from the radiation source, enabling a high dose of irradiation to be delivered to the residual or recurrent tumour in the nasopharynx but a much smaller dose to the 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.[151] 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, accurate application of the radiation source to provide a tumoricidal dose is difficult. To circumvent this problem, radioactive interstitial implants have been used to treat small localised residual or recurrent tumours in the nasopharynx.[152]

Radioactive gold grains (^{198}Au) are the most frequently used radiation source for this purpose. Gold grains can be implanted either transnasally or with the split-palate approach.[143] The split-palate approach gives the surgeon a direct view of the tumour site and enables him or her to implant the gold grains permanently into the tumour with great precision. For tumours localised in the nasopharynx, without bone invasion, this method has provided effective salvage with minimum morbidity.[153] Where gold grain implants were used to treat persistent and recurrent tumours after radiotherapy, the 5-year local tumour control rates were 87% and 63%, respectively, and the corresponding 5-year disease-free survival rates were 68% and 60%.[154] Other studies using intracavitary brachytherapy have also reported success.[155,156]

Nasopharyngectomy

If the residual or recurrent tumour in the nasopharynx is too extensive for brachytherapy or has extended to the paranasopharyngeal space, nasopharyngectomy can achieve salvage in selected patients with localised

	Number of patients	Stage of recurrence	Local control/survival rate	Complications	Treatment-related mortality
Reirradiation (conventional)[142]	706	T1 to T3	5-year survival rate 14%; 10-year survival rate 9%	Late sequelae 24%	1·8%
Stereotactic radiosurgery[75]	18	T1 and T2	2-year local control rate 72%	5·6%	0
Re-irradiation (IMRT)[77]	49	T1 to T4	9-month local control 100%	0	0
Brachytherapy (Gold grain)[143]	106	T1	5-year local control, residual 87%, recurrent 62%; 5-year disease-free survival, residual 68%, recurrent 60%	19%	0
Nasopharyngectomy (Maxillary swing)[144]	109	T1	5-year local control rate 68%, 5-year disease-free survival 54%	25%	0
Nasopharyngectomy (transpalatal)[145]	37	T1 to T3	5-year local control rate 67%, 5-year disease-free survival 52%	54%	3%

IMRT= intensity-modulated radiation therapy.

***Table 4*: Results of different types of salvage therapy for residual or recurrent tumour in the nasopharynx after radical external radiotherapy**

disease. Because of the awkward position of the nasopharynx in the middle of the head, exposure for oncological extirpation of the tumour has presented a difficult technical challenge. Various approaches have been reported, including an infratemporal approach from the lateral aspect;[157] transpalatal, transmaxillary, and transcervical approaches from the inferior aspect;[145,158] and an antereolateral approach.[144] The mortalities associated with these salvage surgical procedures have been low, and since all the patients concerned had previously undergone radical radiotherapy, the associated morbidities in some patients, such as trismus and palatal fistula, were acceptable. As long as the residual or recurrent tumour can be removed adequately, the long-term results have been satisfactory. The 5-year actuarial control of tumours in the nasopharynx is about 65% and the 5-year disease-free survival rate is around 54%.[159,160]

External radiotherapy

For more advanced or infiltrative tumours, a second course of external radiotherapy is needed.[161] A second course of external radiotherapy given concurrently with chemotherapy has been tried; this approach was built on the experience gained from the use of concurrent chemoradiotherapy in primary treatment. This treatment has been reported to give a 5-year actuarial overall survival rate of 26%, although the risk of major late toxicities was significant.[162] The use of precision radiotherapy such as intensity-modulated radiotherapy could improve the therapeutic ratio for local control; promising initial results have been reported,[85] but distant metastases will remain a major issue for patients with local relapse.

Distant metastasis

Cisplatin-based combination chemotherapy is the most effective treatment for metastatic nasopharyngeal carcinoma. Cisplatin and infusional 5-fluorouracil has become the standard treatment with a 66–76% response rate.[163] Several phase II studies of the newer agents have been reported.[164–167] More intensive combinations give a higher response rate, but are also usually associated with increased toxicities.[168–170] None of these combinations has yet been compared with the combination of cisplatin and infusional 5-fluorouracil.

Treatment of metastatic nasopharyngeal carcinomas, mainly with chemotherapy, is essentially palliative, although long-term disease-free survivors have been reported.[171] For selected patients with few metastases, additional locoregional treatment can give extended disease control. Resection of lung metastases can result in longer control for patients in whom the spread of the carcinoma to the lung has been limited.[172] In cases where there has been little spread to the mediastinal nodes, the addition of radiotherapy to chemotherapy could also result in protracted tumour control.[173]

Recent developments

In addition to the novel treatment approaches that are generally applicable to cancers at other sites, the close association between EBV and nasopharyngeal carcinoma gives further opportunities for novel treatment. Strategies targeted at EBV include gene therapy and immune therapy, and the proof-of-principles studies have been done in laboratories. Gene therapy with a novel replication-deficient adenovirus vector in which transgene expression is under the transcriptional regulation of oriP of EBV has been reported.[174] Immune therapy approaches have included therapeutic augmentation of cytotoxic T-lymphocyte responses[175] and adoptive transfer of autologous EBV-specific cytotoxic T-cells.[176] Future studies on the roles of the virus in transformation and functions of EBV latent proteins could help to identify other novel treatment targets.[177]

Conflict of interest statement

We declare that we have no conflict of interest.

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