Over the last decade, we have made significant progress in treating nasopharyngeal cancer. We have achieved a better tumor control rate with conformal radiotherapy and chemotherapy. Surgical salvage treatment has also contributed to helping patients with localized disease in the neck or in the nasopharynx.

To manage nasopharyngeal cancer successfully requires the joint efforts of radiation oncologists, medical oncologists, and otolaryngologists/head and neck surgeons. In the last decade, have we made any progress in understanding the pathogenesis, diagnosis, therapy, and salvage of nasopharyngeal cancer? This article presents the current status of managing this disease.

Nasopharyngeal cancer is a squamous cell carcinoma originating in the fossa of Rosenmüller; it has a high prevalence rate in the southern Chinese population. After years of immigration, this disease has spread to Southeast Asia, the West Coast of North America, and the rest of the world.

DIAGNOSIS

In a 1941 article by Digby et al (Digby was at that time professor of surgery at the University of Hong Kong), the authors noted that patients with nasopharyngeal cancer frequently presented with cranial nerve palsies and cervical lymph node metastases. Currently, patients still frequently present with enlarged cervical lymph nodes. The diagnosis of nasopharyngeal cancer is usually suspected when a Chinese patient presents with one of the clinical features frequently associated with this cancer. The diagnosis is confirmed by biopsy of the primary tumor or by cytologic examination of fine needle aspirates of enlarged neck nodes.

In Hong Kong, serological tests for immunoglobulin A against Epstein-Barr virus (EBV) are performed as a screening procedure for high-risk patients. For patients with elevated EBV titers, an endoscopic examination and biopsy of the nasopharynx are then indicated to detect the cancer in its early stages. Flexible endoscopic examination is useful to assess tumor size and to obtain a biopsy specimen at the designated site. Rigid endoscopic examination provides a better view, to the extent that even submucosal bulges (common in nasopharyngeal cancer) can be seen. Computed tomography and magnetic resonance imaging are performed on patients with a confirmed diagnosis. The former delineates the extent of tumor in the nasopharynx and whether it has affected surrounding bony structures. Magnetic resonance imaging, aside from providing better images of soft tissue, also shows tumor size and penetration in other dimensions because of its multiplanar ability. These imaging studies are important for accurate planning of radiotherapy, which is essential for successful treatment.

TREATMENT

Radiotherapy

External radiotherapy is still the primary treatment for nasopharyngeal cancer. The radiation field normally covers the nasopharynx and both sides of the neck. Re-
cently, with more patients surviving for longer periods, there have been more long-term sequelae of radiotherapy. These include hearing problems related to the inner ear, endocrine manifestations following radiation of the pituitary gland, and cranial nerve palsies. Current advances in radiotherapy are aimed at improving the rate of tumor control and reducing such complications.

The results of radiation treatment for nasopharyngeal cancer in different centers have improved over the years. The use of computed tomography and magnetic resonance imaging provides better imaging of the tumor and thus allows better administration of radiotherapy. Delivering radiation that conforms to the shape of the tumor in the area of the nasopharynx while sparing important surrounding structures is more effective. This conformal radiotherapy also delivers an escalating dose of radiation to the bulky tumor. Shielding the pituitary gland during radiotherapy reduces endocrine functional disturbances without compromising tumor control. In recent years, with the development of stereotactic radiosurgery (another form of conformal radiotherapy), a large dose of radiation can be delivered to a focal area. This may be used as a salvage treatment for recurrent nasopharyngeal cancer following the administration of external radiation. Another application of this technique is to give booster treatment following conventional radiotherapy. The number of patients treated with this technique is small, and the efficacy, especially long term, needs to be evaluated.

Chemotherapy
Chemotherapy has also been used in recent years to manage nasopharyngeal cancer, frequently in conjunction with radiotherapy. Nasopharyngeal carcinoma is sensitive to cisplatin-based chemotherapeutic agents. As 30% of patients with nasopharyngeal cancer have distant metastases or large cervical lymph nodes on presentation to their physician, chemotherapy is a logical option.

Phase 2 studies on the use of induction chemotherapy show improved outcomes. A prospective study of 339 patients with N2, N3 disease showed that at 3 years there was improvement in disease-free survival but not overall survival. The Asian-Oceanian Clinical Oncology Association carried out a prospective, randomized study on 334 patients with stage III or IV nasopharyngeal cancer with cervical lymph nodes larger than 3 cm in diameter. Patients were treated with radiotherapy and chemotherapy or radiotherapy alone. The median follow-up time was 41 months. There was no difference in 3-year overall survival, disease-free survival, or the incidence of distant metastasis.

An intergroup randomized study showed that concomitant chemotherapy was useful. This prospective randomized study was of 185 patients with stage III and stage IV nasopharyngeal carcinoma treated with cisplatin and fluorouracil along with radiotherapy or radiotherapy alone. The 3-year progression-free survival rate was 69% in the group that received concomitant therapies compared with 24% in the group that received only radiation ($P<.001$). The 3-year overall survival was 78% in the group that received concomitant therapies compared with a 47% survival rate in the group that received radiation alone ($P=.005$). The median follow-up time was 31 months. This study is the only prospective randomized study with a positive outcome; however, this is now the standard treatment in the United States. In regions where nasopharyngeal cancer is endemic and where the ethnic population is different, the incidence rates of different types of tumor histology have to be taken into consideration. The sensitivity of undifferentiated carcinoma to radiotherapy without chemotherapy is high in Southeast Asia. Studies are now being carried out in Hong Kong and Singapore to verify the results of this study.

EBV AND NASOPHARYNGEAL CANCER

Suggested causes of nasopharyngeal cancer are the consumption of salted fish, EBV infection, and genetic factors. Cytogenetic studies have shown that there are multiple aberrations in chromosomes 1, 3, 11, 12, and 17 in nasopharyngeal cancer. Loss of genetic material has been seen at defined loci in 3p, 9p, 11q, 13q, and 14q. In contrast with other head and neck cancers, mutations of the p53 and retinoblastoma (Rb) genes were uncommon, and overexpression of the c-myc and Int-2 genes was frequent. The findings of molecular biology studies have some clinical applications. First, the targeted immune response is applicable in nasopharyngeal cancer. Tumor cells express EBV proteins EBNA1, LMP1, and LMP2. Adoptive immunotherapy has been used, employing EBV-specific cytotoxic T cells to kill the EBV, and, because of the association of EBV with nasopharyngeal cancer cells, this therapy also kills cancer cells. On the diagnostic side, molecular biology studies contribute to the identification of tumor markers. Polymerase chain reaction testing can now detect the DNA of EBV in the serum of patients with nasopharyngeal cancer, and the levels of DNA detected have been shown to correlate with stage, recurrence, and metastasis of nasopharyngeal cancer. Because of the cost of polymerase chain reaction testing, its application in clinical situations is still being studied.

Salvage Therapy
Radiation oncologists, medical oncologists, molecular biologists, and surgeons all have a role in managing nasopharyngeal cancer. The role of otolaryngologists/head and neck surgeons is to manage persistent or recurrent tumors after radiotherapy, either in the nasopharynx or in the cervical lymph nodes.

Management of Metastatic Neck Nodes
In our previous study, radical neck dissection controlled neck disease in 66% of patients, which has been confirmed in other studies. Radical neck dissection has to be performed because step serial section studies of radical neck dissection specimens have shown that there are more metastatic lymph nodes in the neck than clinically evident. Tumors in the neck nodes also show extensive infiltration outside the nodes, affecting neck muscle; in roughly one third of patients, tumor was seen...
lying close to the spinal accessory nerve.\textsuperscript{22} As a result, radical neck dissection is recommended as the salvage treatment for localized neck disease.

When disease in the neck is extensive (such as when tumor has infiltrated the skin of the neck or the floor of the neck), further brachytherapy following radical neck dissection has been employed as the salvage procedure.\textsuperscript{23} The neck skin over the tumor is removed during the radical neck dissection, and hollow nylon tubes are placed precisely at the site of the surgery. The cutaneous neck defect is then covered with a flap, such as a deltopectoral flap or a pectoralis major myocutaneous flap. Brachytherapy is then administered through an iridium wire inserted through hollow nylon tubes. Between 1993 and 1996, we performed this procedure in 13 patients with extensive neck disease after radiotherapy. The 3-year actuarial control of neck disease was 60%. All patients survived the operation, and the associated morbidity was low.\textsuperscript{23}

Salvage for Tumor in the Nasopharynx

If the tumor recurs or persists in the nasopharynx after radiotherapy, then salvage procedures are still an option if there is no metastasis. Further radiation treatment or chemotherapy is not effective in eradicating the disease, and the associated adverse effects are significant. Stereotactic radiosurgery is a possible treatment, but its efficacy and long-term complications are not documented. Brachytherapy is another salvage option. Intubating the nasopharynx with cesium is not an easy method of dosimetric evaluation for tumor eradication. For salvage, we have used the insertion of radioactive gold grains as brachytherapy. The procedure was performed under general anesthesia with a mouth gag. The soft palate was split in the midline, and the mucoperiosteum over the hard palate was then elevated and retracted, exposing a recurrent or persistent tumor in the nasopharynx. Radioactive gold grains could then be inserted into the tumor under direct visual contact. With the help of a template, the gold grains could be inserted accurately at desired positions.\textsuperscript{24} To reduce the exposure to radiation of the operating room staff, lead shields were placed in the nasopharynx and around the patient while the palatal wound was closed in layers.

Between 1986 and 1998, we used gold grain implantation for 109 patients, with follow-up of 8 months to 8 years (median, 4.5 years.) The 5-year actuarial control of tumor for persistent disease after radiotherapy was 80%; for recurrent disease, 69%.\textsuperscript{25} All patients had external radiotherapy followed by brachytherapy; the incidence of palatal fistula formation was around 20%. These fistulas can usually be managed conservatively with a dental plate. A palatal flap can also be used to close the fistula in some patients. Our early experience revealed that in some patients, the gold grains fell off early in the postoperative period and were swallowed by the patients: fortunately, there were no serious consequences as the gold grains moved along the bowel.

Since many of the patients who underwent gold grain implantation survive longer after implantation, we have recently noted some long-term adverse effects. One patient developed severe epistaxis; an arteriogram showed a false aneurysm of the internal carotid artery. This was successfully controlled with embolization. Overall, the morbidity associated with gold grain brachytherapy was low. When a persistent or recurrent tumor in the nasopharynx was detected early and was small, split-palate insertion of gold grains was a good means of salvage.

If on presentation the recurrent or persistent tumor is already too large or too bulky for brachytherapy, surgical salvage is another option. Tumor in the nasopharynx can be exposed with the anterior approach, but even with the Le Fort I approach, the tumor is still far from the surface. The lateral approach through the infratemporal fossa passes through many vital structures and results in only limited access. From the inferior approach, the tumor can be seen and exposed, but it is difficult to carry out an oncological resection to remove all the tissue around the tumor.

The anterolateral approach to the nasopharynx exposes the entire nasopharynx and the surrounding area adequately for extirpation of tumor. This approach derived from the fact that after total maxillectomy for carcinoma of the maxilla the nasopharynx is widely exposed. We wondered whether it was possible to swing the maxilla laterally and at the same time keep it attached to the anterior cheek flap. After the tumor in the nasopharynx was removed, the maxilla could be swung back and fixed to the facial skeleton.\textsuperscript{26} We have tried the procedure in preserved and in fresh cadavers, and found that it was feasible. The first nasopharyngectomy with this anterolateral approach was performed in 1989 on a 35-year-old man who had recurrent nasopharyngeal carcinoma after external radiotherapy and brachytherapy. From 1989 to 2000, we performed 78 salvage nasopharyngectomies. Although presurgical examinations showed that curative resection was possible, a clear tumor margin was achieved in only 60 patients. The remaining 18 patients continued to have microscopic tumor either on the internal carotid artery or spilling through the musculoskeletal crevasse. All patients survived the operation and were discharged from the hospital. These patients were followed up for 6 months to 10 years (median, 3 years); in the 60 patients who had a curative resection, the 5-year actuarial tumor control rate in the nasopharynx was 62%, while the 5-year actuarial disease-free survival rate was only 49%.\textsuperscript{27} A frequent question is whether such a wide exposure is necessary for the salvage procedure. Could the tumor be removed with laser or could cautery be applied through the nose or transpalatally? Our step serial whole-organ section of 19 resected nasopharyngeal specimens showed that 90% of the tumor affected the eustachian tube cartilage, and over 90% of the tumor showed extensive submucosal infiltration.\textsuperscript{28} It is necessary to remove all the related structures in the nasopharynx through a wide aperture such as that used in the anterolateral approach.

This was a highly selected group of patients who had recurrent or persistent tumor after radiotherapy with tumors that were localized enough to allow a curative resection. Following surgery, over 80% of them had some degree of trismus and 20% of them developed a palatal fistula, which may have been related to their previous ra-
diotherapy and salvage surgery. The palatal fistula can be managed conservatively with a dental plate or closed with a palatal flap. Two patients developed facial sinus related to the titanium plate; both of these healed after removal of the screws and plate.

Variations of the resection technique include removing the posterior part of the nasal septum to allow resection of tumors that extend to the opposite side. Removing the anterior wall of the sphenoid sinus also contributes to improving the resection margin. With this wide exposure, the paranasopharyngeal lymph nodes, if affected by the tumor, can be removed under direct visual contact. Even a tumor situated close to the internal carotid artery can be removed safely. As all these patients had large doses of radiation prior to the salvage surgery, osteoradionecrosis was a risk when too much bare bone was left exposed after surgery. The skull base may also undergo necrosis. We treated this complication in one patient who underwent radical salvage nasopharyngectomy at another institution. We used a microvascular free muscle flap to fill the defect in the skull base, and the patient recovered.

The anterolateral approach for nasopharyngectomy provides a direct and wide exposure of the entire nasopharynx and the surrounding area. The operation is not difficult to perform, and the associated morbidity is low. It should be considered for those patients in whom radiotherapy fails.

In conclusion, over the last decade, we have made progress in the diagnosis, management, and salvage therapy of patients with nasopharyngeal cancer. Credit is due to all the research workers, oncologists, surgeons, and other personnel worldwide who work in this field.

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Corresponding author and reprints: William I. Wei, MD, Department of Surgery, University of Hong Kong Medical Center, Queen Mary Hospital, Hong Kong (e-mail: hrmsww@hkucc.hku.hk).

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