

## Combined therapy for carcinoma of the nasopharynx: a report of 49 cases

SHENG HONGZHENG, JIA HAIXIA (Shenzhou, China)

### Abstract

From April, 1986 to June 1989, 49 patients (29 male, 20 female) aged 20 to 70 years old who developed carcinoma of nasopharynx (included 15 with relapses) were treated with neoadjuvant regional chemotherapy, followed by radiotherapy, or cryosurgery and radiotherapy.

Thirty-three of the patients had squamous cell carcinoma with poor differentiation, four with well differentiated squamous cell carcinoma were included. Tumours were treated with three modalities: (1) Induction regional chemotherapy with temporal artery catheterization as well as superselective intra-arterial chemotherapy of the femoral artery (chemotherapeutic agents: pingyangmycinum (P), Cisplatin (D), Vincristine (V), Methotrexate (M) and P.D.M. programmes); (2) Liquid nitrogen cryosurgery in 25 cases; (3) Radiotherapy was carried out for two weeks after cryosurgery or immediately applied to those without cryosurgery after chemotherapy.

The data showed CR (complete response—all tumour gone) and PR (partial response—more than 50 per cent reduction) in 40 cases (81.6 per cent) and NR (no response—less than 50 per cent or no response) in nine cases (18.3 per cent) following regional chemotherapy. All of the patients were followed up for more than one year, and 48 of them survived (97.9 per cent). Thirty-five cases were followed up over two years and 28 of them survived (80 per cent). Twenty cases were followed up over three years, and 12 of them survived (60 per cent).

The effect of regional chemotherapy and cryosurgery in combined treatment for carcinoma of the nasopharynx is discussed in this paper.

**Key words:** Nasopharynx; Carcinoma

### Introduction

Carcinoma of the nasopharynx is a common malignant tumour in China and south east Asia. Traditionally, radiotherapy has been the chief treatment for carcinoma of the nasopharynx, which cured many patients. In 1974, tumour hospital of Zhongshan University reported that the survival rate of patients with cancer of various stages reached 46.3–49.5 per cent five years after treatment by radiotherapy (Guan Zhongzheng, 1987)<sup>1</sup>, but five-year survival rate should still be investigated. From April, 1986 to June 1989, 49 cases of carcinoma of nasopharynx (including 15 patients with relapses) were treated with neoadjuvant regional chemotherapy, followed by radiotherapy, or cryotherapy and radiotherapy; 45 of them were Stage III or Stage IV (92 per cent of the total number). Of the 20 followed up for more than three years, 12 survived (60 per cent). There is hope for the combined treatment to improve survival, although the five-year rate remains to be observed.

### Materials and methods

#### Sex and age

Forty-nine patients (29 male, 20 female) with ages

ranging from 20 to 70 (Table I), more than half of whom were observed, were aged 41–60 years (55 per cent).

#### Pathology

Pathological findings with regard to the carcinoma of the nasopharynx appear in Table II.

#### Symptoms and signs

(1) Metastasis of lymph nodes in the neck: 34 cases were seen to have metastatic lymph nodes in the neck in this group (69.3 per cent), among whom 18 cases were bilateral, most frequent were the superior group of deep cervical nodes, with only five cases of lymph nodes

TABLE I  
DISTRIBUTION OF CARCINOMA OF NASOPHARYNX BY AGE

Years	Number
<30	5
31–40	10
41–50	13
51–60	14
>60	7

TABLE II  
DISTRIBUTION OF CARCINOMA OF NASOPHARYNX BY PATHOLOGY

Pathological finding	Number
Pathological type	
Squamous cell carcinoma (poorly differentiated)	33
Squamous cell carcinoma (well differentiated)	4
Undifferentiated carcinoma	11
Cystadeno carcinoma	1
Original site of neoplasms	
Lateral wall (including fossa of Rosenmuller)	31
Postero-superior wall	14
Anterior wall	4
Appearance of neoplasms	
Nodular form	20
Cauliflower form	12
Infiltrative growth	16
Infiltration of the submucosa	1
Direction of expansion	
Cranial nerve involvement	15
Cervical lymph nodes metastases	21
Mixed form	13
Staging	
T <sub>1</sub>	0
T <sub>2</sub>	2
T <sub>3</sub>	19
T <sub>4</sub>	26

around the accessory nerve who had relapses after radiotherapy.

(2) Symptoms of the ears and nose: the most common symptoms of nasopharyngeal carcinoma was mild nasal or postnasal bleeding (16 cases), and 12 had serous otitis media.

(3) Cranial nerve symptoms: 18 patients had severe headaches and invasion of the cranial nerves (Vth and VIth cranial nerves invaded in 12 cases). The base of the skull was destroyed in four cases; the VIIth and VIIIth cranial nerves were involved in two cases and hoarseness and palsy of the XIIth nerve occurred as the IXth, Xth and XIIIth cranial nerves were invaded by lymph node spread.

(4) Distant metastases: two were found to have distant metastases; X-ray plain films showed that one of the patients had metastases to the lung and another to the liver.

#### Regional chemotherapy

(1) Arterial catheterization: A. The superficial temporal artery was primarily selected and the facial artery was selected in cases where the superficial temporal artery was obstructed. The length of catheterization was about 10–11 cm so that it was below the opening of the ascending pharyngeal artery; B. 15 doses of intra-arterial chemotherapy were given to each patient, and seven or eight times bilateral catheterization was needed if the patient had bilateral metastases of the cervical lymph nodes or widespread involvement of the nasopharynx; C. Superselective intra-arterial chemotherapy of the femoral artery: catheterization directly into the ascending pharyngeal artery and internal maxillary artery after angiography, three cases had femoral artery catheterization in the group.

(2) Chemotherapy regime: Programmes applied were as follows:

A. PDVM (Pingyangmycinum (P), Cisplatin (D), Vincristine (V), Methotrexate (M)) therapy: First, cell cycle non-specific agents, such as Pingyangmycinum (20 mg/m<sup>2</sup> each time); Cisplatin (DDP) (30–50 mg/m<sup>2</sup>

each time) were administered (to a total dose of 100 mg and 150 mg); Second, cell cycle specific agents such as Vincristine (2 mg each time), high dose—Methotrexate (500–1000 mg each time) were given, and two hours later calcium leucovorin was injected intramuscularly for three days for detoxication to a dose of 12 mg of four times daily. Eleven cases were treated this way in this group.

B. Pingyangmycinum—cisplatin-nitrocaphar therapy: this therapy was applied to 10 cases in earlier stage in this group, PM (20 mg/m<sup>2</sup> each time), Cisplatin (30–50 mg/m<sup>2</sup> each time) and Nitrocaphan (AT-1258) (40–60 mg/m<sup>2</sup> each time) were administered twice a week to a total of 15 doses.

C. PDM therapy: this therapy was essential when calcium leucovorin was deficient, pingyangmycinum (20 mg/m<sup>2</sup> each time), cisplatin (30–50 mg/m<sup>2</sup> each time) and methotrexate (30 mg/m<sup>2</sup> each time) were given to 25 cases in this group twice a week to a total of 15 doses.

D. PD Adm (Adriamycin) therapy: this therapy was used with superselective femoral artery catheterization. The drugs were given once at a dose of pingyangmycinum 30 mg, cisplatin 100 mg and Adm 60 mg, 60 minutes after starting a two hour i.v. hydration programme with 2000 ml of fluid. Sodium hyposulphate 12 g, Maxolon 40 mg and diphenhydrazine 150 mg were once given i.v. for detoxication. Three cases were treated this way in this group.

#### Liquid nitrogen cryosurgery

(1) Patients for cryosurgery were given liquid nitrogen cryosurgery of the nasopharynx under endotracheal anaesthesia in the Trendelenburg position.

(2) Two catheters were put separately into the nares being taken out through the oral cavity and bound tightly so as to lift the soft palate up and expose the nasopharynx before cryosurgery.

(3) The head of cryosurgical apparatus was inserted from the oropharynx into the nasopharynx and its direction was adjusted according to the pre-operative examination, so that it touched the tumour site as close as possible.

(4) Spraying or touching the cryoprobe on the tumour site was carried out three or four times, for 3–5 min each time. The area of frozen–thawed tissue was generous so that the whole cancerous focus was included. The direction of the head of the cryosurgical apparatus was adjusted for separate cryosurgery if the cancerous focus was of considerable size.

(5) In order to avoid freezing the soft palate or the respiratory tract, the hypopharynx cavity was packed with dry gauze and the head of the cryosurgical apparatus was wrapped in oil-gauze; 25 patients in this group had cryosurgery.

#### Radiotherapy

(1) Radiotherapy was normally applied two weeks after cryotherapy but the patients who had not had cryosurgery were treated immediately after regional chemotherapy.

(2) The source of irradiation was cobalt<sup>60</sup>, and the field of irradiation was routinely designed. 60–70 Gy was given to the primary site and 40–50 Gy to metastatic foci in the cervical lymph nodes.

## Results

Of all the cases with carcinoma of nasopharynx, 24 were treated with regional chemotherapy and radiotherapy (*i.e.* two-combination), and 25 with regional chemotherapy, cryosurgery and radiotherapy (*i.e.* three-combination). The results were as follows:

### Curative effect of regional chemotherapy

(1) The standard of effectiveness: the curative effect was divided into three levels according to the proposal put forward by the Research Association of Head and Neck Surgery.

A. Obvious response: it included complete, more than 2/3 or more than half of the tumour had been reduced by treatment; B. Minor response (MR): tumour response to treatment less than 50 per cent, but more than 30 per cent; C. No response (NR): tumour reduction less than 30 per cent or undetermined.

(2) Results (see Table III): it was assessed in all of the patients with this therapy (including 15 cases with relapse). The obvious response was 81.6 per cent (40/49), much higher than that for treatment for cancer of the nasal cavity and sinuses in our department (14/35), (Sheng Hongzheng, 1989a).

### Follow-up

All the patients were followed-up for one to four years, and the results are shown in Table IV.

According to Table IV, 20 per cent died within two years, and 40 per cent died within three years. One died of obvious destruction of the skull base and massive haemorrhage one year after treatment. Of the 35 followed-up for two years, six died, four of relapse after radiotherapy; one died of obvious destruction of the skull base and another was a 70-year-old patient. Of the 20 followed-up for more than three years, 12 survived; eight died, and one died one year after treatment; five died after two years and two died after three years. Local relapse was mainly responsible for death.

## Discussion

### Action of regional chemotherapy in the combined treatment for carcinoma of nasopharynx.

(1) Regional chemotherapy had obvious short-term effects.

The obvious response amounted to 81.6 per cent in this group. The faith of the patients was greatly increased in the treatment when the tumour disappeared or obviously reduced within two weeks of treatment. It has been reported that regional chemotherapy can be applied to those tumours affecting cranial nerves, but our study shows that it is satisfactory in all types.

Regional chemotherapy is likely to be effective although carcinoma of nasopharynx is quite infiltrative, but locally invasive. It is possible that clinical metastases were decreased and the survival period prolonged because regional chemotherapy reduced local as well as tiny metastatic foci.

(2) The action of radiotherapy can be sensitized by regional chemotherapy. As an adjuvant before radiotherapy, the oxygen deficient cells can be oxygenated and sensitized by regional chemotherapy thereby obtaining better efficacy.

Fifteen with relapses (31 per cent of the total number) also benefited from regional chemotherapy in this group. It has been amply confirmed that regional chemotherapy is an important way to treat carcinoma of nasopharynx (Guan Zhongzheng, 1987; Sheng Hongzheng, 1989a).

Radiotherapy can be all the more effective because it can be sensitized by regional chemotherapy.

(3) Regional chemotherapy can help radiotherapy.

Many patients with carcinoma of nasopharynx have such big cervical tumours that, without chemotherapy, the irradiated area has to be enlarged, which results not only in a greater reaction to radiotherapy but also poorer effect.

In this group there was one patient with undifferentiated carcinoma of nasopharynx, whose bilateral cervical lymph node metastases gave a 'bull neck' appearance, with two extensive areas of ulceration. Radiotherapy in another hospital was not effective, but after two doses superselective intra-arterial chemotherapy via the femoral artery, his cervical tumour disappeared and the ulceration areas healed; radiotherapy was then successfully used with good effect. This suggests that chemotherapy can, on the one hand, make radiotherapy easier to carry out in those who are not suitable for initial radiotherapy, and, on the other, reduce the dosage and reaction of radiotherapy.

(4) Regional chemotherapy should be applied before radiotherapy. Untreated patients have a better blood supply to local tumour, which is quite beneficial to the absorption and distribution of anti-cancer drugs. As a result, local concentration of medicine, compared with general chemotherapy, is greatly increased and the general toxic reaction reduced.

The obvious effects in this group amounted to 82 per cent, which is much higher than that for systemic chemotherapy. The good results seem related to the fact that most of the patients were previously untreated.

Clinicians are still disputing whether regional chemotherapy can prolong the survival time of those with late stage, cancer of head and neck but there is insufficient evidence to negate the function of chemotherapy for carcinoma of the nasopharynx. In cases where regional chemotherapy was used, it is quite hoped to achieve good results and thereby increase the survival rate of advanced carcinoma of the nasopharynx.

TABLE III  
TREATMENT AND EFFECTIVENESS

Treatment	No. of cases	CR	PR	MR	NR
PDVM	11	3	7	1	0
PDM	25	6	15	4	0
PDA <sub>t</sub>	10	2	5	3	0
PdAdm	3	1	1	1	
Total	49	12 (25%)	28 (57%)	9 (18%)	

TABLE IV  
RESULTS OF FOLLOW-UP

Time	No. of cases	Survivals	Survival rate (%)
Over 1 year	49	48	97.9
Over 2 years	35	28	80.0
Over 3 years	20	12	60.0

*The action of cryosurgery in combination treatment for carcinoma of the nasopharynx (Ablin, 1980; Sheng Hongzheng, 1989b)*

(1) Cryosurgery was especially helpful in eliminating the original focus. Accordingly recurrence of carcinoma in the nasopharynx is most likely to be a relapse of the original focus. Biological sensitivity to freezing is characteristic of a malignant tumour. Cryosurgery to the carcinoma of nasopharynx may effectively eliminate the original focus, and, when the dosage and time are both sufficient is also quite beneficial in the elimination of carcinomatus destruction of the base of skull.

Based on the concealment and irregularity of carcinoma of the nasopharynx, we suggest that cryosurgery is the best type of operation for elimination of the original focus, even in cases of relapse.

(2) Cryosurgery can increase the effectiveness of radiotherapy. The healing period of cryosurgery usually lasts three weeks. If radiotherapy is carried out two weeks after operation before the recrudescence of the tumour

remnant, the curative effect will be reinforced and the possibility of recurrence greatly decreased. At the same time, the dosage of radiotherapy can be properly reduced so as to lessen the reaction to irradiation.

(3) The immune response brought about by cryosurgery can help prevent recrudescence and distant metastasis of the tumour.

#### References

- Ablin R. J. (1980) *Handbook of Cryosurgery*, 1st edn. Marcel Dekker, Inc., New York, p 3–12 and 69–79.
- Guan Zhongzheng (1987) Chemotherapy for carcinoma of nasopharynx. In *Recent advances in cancer chemotherapy*, 1st Edition. (Sen Yan and Han Rui, eds.), San Dong Scientific & Technical Publishers, Ji Lan, p 320–325.
- Sheng Hongzheng (1989a) Neoadjuvant regional chemotherapy for head and neck—a report of 80 cases. *Chinese Journal of Cancer* **8(6)**: 431.
- Sheng Hongzheng (1989b) The action of cryosurgery in the combination of later malignant tumour of cavity and paranasal sinuses. In *Chinese association of refrigeration etc. Advances in cryosurgery*, 1st Edition. International Academic Publishers. Beijing: Oxford: New York, p 562–566.

Address for correspondence:  
Sheng Hongzheng,  
Department of Otolaryngology,  
Futian Hospital,  
Shenzhen City,  
Guang Dong Province, 518033,  
China.