Acta Radiologica Oncology 22 (1983) Fasc. 1

FROM THE DEPARTMENT OF RADIATION ONCOLOGY, CANCER INSTITUTE, CHINESE ACADEMY OF MEDICAL SCIENCES, BEIJING, CHINA.

RADIATION THERAPY OF RECURRENT NASOPHARYNGEAL CARCINOMA

Report on 219 patients

J.-H. YAN, Y.-H. HU and X.-Z. GU

About one half to two thirds of all patients with nasopharyngeal carcinoma will ultimately die of recurrence or metastases in spite of intensive initial irradiation which may give a 5-year survival of 30 to 50 per cent (PAN et coll. 1974, HOPPE et coll. 1976, Ritan Hospital Monograph 1979, Shanghai Hospital Monograph 1979, ZHAO & CHEN 1980). Whether patients with recurrent lesions should be treated or not is still a matter of controversy. In order to elucidate this problem, 219 patients with recurrences and metastases after initial treatment were analysed. The aim of this retrospective analysis was to evaluate the biologic behaviour of recurrent nasopharyngeal carcinoma (NPC) and the value of and suitable technique for retreatment.

Material

From March 5, 1958 to December 31, 1972, 811 patients with NPC were admitted for irradiation (Table 1). During their follow-up, 266 patients developed recurrences with or without metastases and were re-admitted for further treatment. In 47 of these 266 patients the recurrence developed so recently that they have not yet been followed for 5 years after the retreatment. The remaining 219 patients make up the material for the analysis. Of these 219 patients distant metastases had already developed in 57 when they received the second course of treatment but in 162 patients the disease was still confined to the head and neck region. Thus, theoretically, local irradiation possibly still ought to eradicate the disease.

Seventy-four patients had recurrences in the nasopharynx, all proved by biopsy. Among 68 patients with recurrences in the neck nodes, the recurrences were confirmed at histopathologic or cytologic examination in 50, including 3 treated by lymph node excision. In the other 18 patients the recurrences were either diagnosed clinically or proved by the final outcome of the disease. In totally 124 patients recurrences proved by histopathologic or cytologic examination developed, which made up 77 per cent (124/162) of those without distant metastases. Recurrences in the skull base were diagnosed by bone erosion, cranial nerve involvement or excruciating pain in the head. One patient with a second primary tumour (esophageal carcinoma) was excluded from this analysis.

The sites of the recurrent lesions appear in Table 2. Among various sites of recurrence and their combinations, recurrence in the neck was the most common, amounting to 42 per cent (68/162) of the whole series. A single recurrence occurred in 62 per cent (100/162), while 23 per cent (37/162) had simultaneous recurrences at two sites and 15 per cent

Accepted for publication 7 October 1982.

(25/162) at three sites at the same time. These figures indicate a tendency to single recurrence of NPC.

The time intervals between initial treatment and retreatment are shown in Table 3. Most of the recurrences (90%, 146/162) occurred within 3 years after the initial irradiation. In 53 patients the recurrence appeared after the third year. In 47 patients the recurrence appeared so recently that they have not yet been followed for 5 years after retreatment. In 16 patients, however, the observation time after retreatment was 5 years or more.

Table 1

Data on recurrent nasopharyngeal carcinoma

Evolution	No. of patients
First course (March 1958–Dec. 1972)	811
Retreatment	266
Retreatment, followed for less than 5 years	47
Retreatment, followed for more than 5 years	219
Recurred with distant metastasis	57
Recurred in head and neck	162

Table 2

Site of recurrence

Site	No. of patients	Per cent
Nasopharynx	20	12
Neck	68	42
Base of skull	12	8
Nasopharynx and neck	13	8
Nasopharynx and base of skull	16	10
Neck and base of skull	8	5
Nasopharynx and neck and base of skull	25	15
No distant metastasis	162	100
Distant metastasis	57	
Total	219	

Table 3

Interval between first course and development of recurrence

Interval	No. of patients	Per cent
Less than 3 years	146	90
More than 3 years	16	10
Total	162	100

Table 4

Dose of radiation for recurrent nasopharyngeal carcinoma

Dose	No. of patients	Per cent
Less than 50 Gy	71	44
50 to 70 Gy	91	56
Total	162	100

Method of irradiation

All the patients had initially received a full course of irradiation. As regards retreatment, 38 patients were treated by high energy electron beams, 4 by telecobalt plus intracavitary radium, one by intracavitary radium only, and 119 by telecobalt, in some cases supplemented by orthovoltage roentgen rays. As a routine, multiple and small convergent beams were used. For lesions in the nasopharynx, bilateral pre-auricular fields with inclusion of the adjacent part of the skull base, in a majority of patients supplemented by infra-orbital fields, were used, and ^{60}Co (SSD 75 cm) or roentgen rays (220 kV, 15 mA, FSD 40 cm, filter 1 mm Cu + 1 mm Al or 0.4 mm Sn + 0.25 mm Cu + 1 mm Al). Some patients also received supplementary treatment by either intracavitary roentgen rays (120 kV, 15 mA, FSD 30 cm, filter 4 mm Al) or by intracavitary radium mould during the end of the treatment. When 25 to 35 MeV electron beams were used only the pre-auricular fields were irradiated. For the irradiation of the neck region, varying fields were used, as tangential telecobalt fields supplemented by small localized fields for ^{60}Co or roentgen irradiation sometimes further reduced in size at the end of the treatment. Usually, 30 to 70 Gy were given. Irradiation was given until the mass in the neck either disappeared completely or changed into a plaque of soft and elastic tissue with unclear boundaries, which was regarded as a possible eradication of the metastasis. Sometimes, the mass first became soft and reduced in size, but as the dose approached a curative level it became firm again, which might have been due to fibrosis. The tumour dose was in 44 per cent of the patients below 50 Gy and in 56 per cent above 50 Gy (Table 4). For lesions in the nasopharynx and the base of the skull meticulous care was taken concerning size and direction of the beams, in order to avoid irradiation of an excessive volume of normal tissue. The changes in the lesion were observed and recorded weekly. Usually, the treatment continued until the lesion in the nasopharynx had clinically disappeared

Table 5

Result of treatment of recurrent nasopharyngeal carcinoma

Disease	No. of patients	5-year survival		5-year cure without evidence of disease	
		No.	Per cent	No.	Per cent
Localized in head and neck	162	37	23	23	14
With distant metastasis	57	2*	3	0	0
Total	219	39	18	23	11

* 1 with axillary metastases, 1 with mediastinal metastasis.

Table 6

Complications and sequelae of retreated nasopharyngeal carcinoma (patients who survived for more than 5 years)

Complications and sequelae	Only one course (n=210)		Retreated (n=85)	
	No.	Per cent	No.	Per cent
Radiation myelitis	19	9	10	12
Radiation encephalopathy	18	9	7	8
Cranial nerve palsy	10	5	6	7
Osteonecrosis	4	2	2	2
Soft tissue necrosis	5	2	4	5
Subcutaneous fibrosis	8	9	14	16
Otitis media	44	21	16	19
Trismus	24	11	25	29

and following this a booster dose of 10 to 20 Gy was added. For recurrences limited to the base of the skull in the middle cranial fossa, telecobalt or electron beam was given through small bilateral fields also including the roof of the nasopharynx. If the posterior cranial fossa was involved, the fields were enlarged accordingly. In the second half of the course, supplementary treatment was sometimes given through posterior auricular or supra-orbital oblique fields. The total dose was 50 to 70 Gy in 6 to 7 weeks.

Results

The patients could be divided into 5 categories: (1) Patients surviving for more than 5 years after retreatment without evidence of tumour. (2) Patients surviving for more than 5 years but with recurrence after the fifth year. (3) Patients with recurrence within 5 years after the retreatment who died more than 5 years after this treatment. (4) Patients who died with recurrence within 5 years after retreatment. (5) Patients with recurrence within 5 years but who were alive without signs of disease at 5 years after one or more repeated courses of treatment.

In the following analysis the 5-year survival is reported for all the patients after the first retreatment although it is fully realized that some patients may die of the disease after this period and also that the survival of a patient for 5 years or more may have other causes than this retreatment, such as biologic behaviour of the tumour, or repeated courses of treatment.

The overall 5-year survival and cure rates (without evidence of tumour) are given in Table 5. Of the patients with distant metastases only 2, with metastases in the axilla and in the mediastinum, respectively, attained a 5-year disease-free survival. All patients with hematogenous spread died within 5 years after the retreatment. Of the patients with recurrences confined to the head and neck region 23 per cent (37/162) survived for more than 5 years and 14 per cent (23/162) of them without evidence of tumour.

The incidence of complications and sequelae was compared with a series of 210 patients who had received only one course of irradiation during the same period and survived for more than 5 years (Table 6). The most serious complication, radiation myelitis, increased from 9 to 12 per cent. Some other complications, as brain injury, cranial nerve paralysis and radiation induced necrosis of bone, did not seem to be appreciably increased. Soft tissue injury, as subcutaneous fibrosis, trismus, and soft tissue necrosis, was obviously more common in the retreated series.

Table 7

Site of further recurrence of nasopharyngeal carcinoma after second course of irradiation

Site of second course	No. of patients	Skull base		Neck		Nasopharynx		Distant site	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Nasopharynx	20	0		0		16	80	1	5
Neck	68	0		37	54	48	71	2	3
Base of skull	12	8	67	0		7	58	1	8
Total	100	8	8	37	37	71	71	4	4

Discussion

MARTIN & BLADY (1940) were of the opinion that recurrent NPC is not worth treating and that the result would be no better than if the patient was left alone. HOPPE treated 13 patients with recurrence and found only 2 who survived for more than 5 years. Both these patients finally died of the disease. On the other hand, WANG & SCHULZ (1966) and FU et coll. (1975) reported 5-year survival rates of 34 and 41 per cent, respectively, for recurrent NPC. MCNEESE & FLETCHER (1981) reported that 16 of 30 patients with cranial nerve paralysis survived for a long time. ZHAO & CHEN also reported in Shanghai that 13.5 per cent of patients with recurrent lesions survived for more than 10 years. All the authors mentioned were of the opinion that retreatment of NPC is of definite value.

When collecting the present series 276 patients with recurrence of NPC were found who for various reasons did not receive any specific treatment. Only one of these patients was alive at the end of the fifth year after the appearance of the recurrence—a 5-year survival of 0.36 per cent. The overall 5-year survival rate for the treated patients in the present series was 18 per cent (39/219), and if those with distant metastases were excluded the 5-year survival was 23 per cent (37/162). The difference in survival between the untreated and the treated group may be regarded as an argument for retreatment of recurrent NPC, even if these 2 series are not completely comparable.

Recurrences in the nasopharynx were often localized while recurrences in the neck were often combined with nasopharyngeal lesions. Also recurrences in the base of the skull were, as expected, often combined with lesions in the nasopharynx (Table 7). Of 100 patients with a single recurrence 20 had lesions confined to the nasopharynx. Further recurrences after retreatment were very common in these patients (80%, 16/20), but these recurrences also were confined to the nasopharynx. This localized behaviour gives possibilities for eradication of the lesions with irradiation by multiple small convergent beams directed against the nasopharynx and without the prophylactic irradiation of the neck which is routinely practised for new patients. In patients with recurrent lesions in the neck or in the skull base, simultaneous recurrence in the nasopharynx was very common (48/68 and 7/12, respectively). The nasopharynx should therefore be care-

Table 8

Prognostic factors of retreated nasopharyngeal carcinoma

Prognostic factors	5-year survival	
	No.	Per cent
Single recurrence		
Nasopharynx	5/20	25
Neck	23/68	34
Base of skull	3/12	25
Multiple recurrences		
Nasopharynx and neck	1/13	8
Nasopharynx and base of skull	1/16	6
Neck and base of skull	1/8	12
Nasopharynx and neck and base of skull	3/25	12
Distant metastases	2/57	3.5
Interval of recurrence		
Less than 3 years	31/146	21
More than 3 years	6/16	38
Dose		
Less than 50 Gy	14/71	20
50 to 70 Gy	23/91	25
Surgery for neck recurrence		
Lymphadenectomy plus 30 Gy	3/3	–

fully examined in all patients with recurrent disease outside the nasopharynx, and blind biopsies from the nasopharynx are indicated. Prophylactic irradiation of the nasopharynx may even be considered.

Factors related to the prognosis of recurrent NPC are listed in Table 8. Patients with hematogenous spread had a bad prognosis and none of them survived long. Patients with a single, localized recurrence had much better prognoses than patients with recurrences in multiple sites. The difference was statistically significant ($p<0.01$). For recurrences in the skull base the prognosis was not entirely hopeless, as 8 of 61 (13%) patients survived for more than 5 years. The present experiences agree well with that of MCNEESE & FLETCHER.

The significance of the interval between the primary treatment and the appearance of the recurrence is demonstrated in Table 8. The longer this interval was, the better was the prognosis. Of patients with recurrence within 3 years 21 per cent (31/146) survived for more than 5 years, compared with 6/16 (38%) of those with recurrence after the third year. This difference was not, however, statistically significant ($p>0.05$). A better prognosis for patients with a long interval between the primary treatment and the recurrence might be explained by a less malignant biologic character or a better repair of the normal tissues, of which the latter factor could have facilitated a second course of irradiation.

A higher dose gave better results (Table 8). The optimum dose seemed to lie above 50 Gy and preferably around 60 Gy. In the group treated with a dose below 50 Gy, 3 patients developed recurrences in the neck. They were treated by lymphadenectomy followed by a supplementary radiation dose of 30 Gy. These 3 patients survived uneventfully for more than 5 years. If these 3 cases were excluded the result in the low dose group would have been much poorer. XU et coll. (1981), in this hospital, reported a series of recurrences in the neck. They treated the patients primarily with lymphadenectomy and, if the histopathology was positive, supplementary irradiation. They obtained a 5-year survival of 50 per cent. Lymph node excision plus postoperative irradiation was thus an effective mode of treatment of neck recurrences.

In treating recurrences in the nasopharynx the use of multiple, carefully directed beams is suggested. In the present series, 20 patients had recurrences confined to the nasopharynx. They were treated with this technique and (25%) survived for more than 5 years. The size of the portal should be small and the beams carefully directed in order to avoid injury of the brain stem and the spinal cord. The common portals used for this technique were: pre-auricular, infra-orbital and an intracavitary roentgen ray cone. Intracavitary radium application was also used in combination with other methods or as single treatment. When ^{60}Co beams were used a combination of multiple portals was better than pre-auricular fields alone, as regards postirradiation complications. Among 6 patients irradiated solely through pre-auricular portals, all developed trismus, which in 2 was severe. Five other patients for whom the pre-auricular fields were supplemented by an intracavitary roentgen ray cone, 3 survived for more than 5 years without any apparent difficulty in mastication or evidence of soft tissue injury in the maxillofacial region.

For recurrent lesions in the neck, various portals including anterior and posterior tangential fields, large regional perpendicular fields, and local small booster fields were used. Among 68 patients with lesions in the neck only, 34 per cent (23 patients) survived for more than 5 years. Only large perpendicular fields were used in 25 patients. Three of these developed radiation myelitis. Therefore, it is recommended that the use of large, perpendicular portals in the neck should be avoided throughout the whole course of the retreatment. Due to previous irradiation and the extent of the neck recurrence the treatment must be highly individualized and great care must be taken in order to avoid undue injury to the spinal cord, skin and other structures. The treated volume should be reduced as the dose increases and the tumour shrinks. A split-course technique may sometimes be preferable, with 2 or 3 courses. Lymph node excision should always be considered if the mass is movable or becomes movable after irradiation.

Conclusion

(1) After intensive irradiation of recurrences from nasopharyngeal carcinoma, confined to the head and neck region, a 5-year survival of 23 per cent was obtained. If the recurrence was located in the neck the 5-year survival was 34 per cent and if confined to the nasopharynx 25 per cent.

(2) A high tumour dose (about 60 Gy) was required, given through multiple small portals and with careful beam directioning.

(3) For recurrences in the neck, surgery was sometimes the only method for cure. Lymphadenectomy supplemented by a lower radiation dose should be considered if the mass in the neck is movable.

(4) Recurrences in the neck, especially when repeatedly occurring, often seemed to be combined with a local recurrence in the nasopharynx.

SUMMARY

Recurrent nasopharyngeal carcinoma (NPC), if left untreated, has a 5-year survival of less than one per cent. In contrast, the overall 5-year survival in a treated series of patients was 18 per cent. Excluding those with distant metastases at the beginning of the retreatment, the 5-year survival was 23 per cent. If the recurrence was limited to the neck, a 5-year survival of 34 per cent was obtained and if it was confined to the nasopharynx the 5-year survival was 25 per cent. High doses (about 60 Gy), using multiple narrow beams, carefully directed, were required. For recurrences in the neck, lymph node dissection supplemented by a lower radiation dose should be considered. Surgery was sometimes the only possible method for cure, when recurrence occurred in the neck nodes. Recurrences in the neck, especially when repeatedly appearing, most often were combined with a local recurrence in the nasopharynx.

REFERENCES

FU K. M., PHILLIPS T. L. and NEWMAN H.: Treatment of locally recurrent carcinoma of the nasopharynx. Radiology 117 (1975), 425.

HOPPE R. T., GOFFINE D. R. and BAGSHAW M. A.: Carcinoma of the nasopharynx. Eighteen years' experience with megavoltage radiation therapy. Cancer 37 (1976), 2605.

MARTIN H. B. and BLADY J. V.: Cancer of the nasopharynx. Arch. Otolaryng. 32 (1940), 692.

MCNEESE M. D. and FLETCHER G. H.: Retreatment of recurrent nasopharyngeal carcinoma. Radiology 138 (1981), 191.

PAN G. Y., HUANG G. Y., MAO Z. D., ZENG Q. X. and ZHONG Z. A.: Radiation treatment of nasopharyngeal cancer. Comparison of split and continuous regime. Chin. med. J. 54 (1974), 687.

RITAN HOSPITAL: Radical radiotherapy in 811 cases of NPC. (In Chinese.) Monograph of the Third National Symposium on Nasopharyngeal Carcinoma, 1979.

SHANGHAI CANCER HOSPITAL: Radiation therapy of NPC. (In Chinese.) Monograph of the Third National Symposium on Nasopharyngeal Carcinoma, 1979.

WANG C. C. and SCHULZ M. D.: Management of locally recurrent carcinoma of the nasopharynx. Radiology 86 (1966), 900.

XU G. Z., LI Q. H., HU Y. H., CAI W. M., QIN D. X., YAN J. H., WU X. L. and GU X. Z.: Lymphadenectomy as a definitive management of the residual lesion in the neck after radiotherapy for NPC. An analysis of 48 patients. (In Chinese.) Chim. J. Oncol. 3 (1981), 123.

ZHAO S. and CHEN C. X.: An analysis of long survival of radiation treatment for NPC. Report on 367 patients surviving longer than ten years. (In Chinese.) Chin. J. Radiol. 14 (1980), 47.