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SQUAMOUS CELL CARCINOMA OF THE NASOPHARYNX

An analysis of failure patterns after radiation therapy

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Abstract

Seventy-seven patients with nasopharyngeal squamous cell carcinoma were treated with irradiation, with or without chemotherapy. Sixty-three (82%) developed a relapse in some part of the body; the first relapse appeared at primary, cervical and distant sites in 45 (71%), 30 (48%) and 12 (19%) of the 63 relapsing patients, respectively. In 22 of the 63 relapsing patients, the first relapse occurred simultaneously in two or more sites. Local recurrence-free survival was higher for the T1 + T2 group than for the T3 + T4 group ($p<0.02$). Cervical relapse-free survival was higher for N0 patients than for N+ patients ($p<0.02$). Distant metastases frequently developed as a component of the first relapse. Distant metastases were more common in N+ patients than in N0 patients. Forty-two patients received adjuvant chemotherapy. Although local recurrence-free survival tended to be higher in patients with chemotherapy than without chemotherapy, survival rates and relapse-free survival rates did not differ in the two groups.

Nasopharyngeal squamous cell carcinoma (SCC) is a rare disease in Japan. This precludes sufficient accumulation of patients during a short period for meaningful conclusions as to optimum treatment. The patterns of failure were therefore studied retrospectively in patients admitted during a long period to this department. Distant metastases were not uncommon as the first relapse of nasopharyngeal SCC. To improve relapse-free survival, a reduction of distant metastases is therefore important, besides improved control of primary and regional disease. Chemotherapy has not been extensively studied in nasopharyngeal SCC. Some of the reported patients had received adjuvant chemotherapy. This treatment was not randomized but it was nevertheless of interest to compare control rates in patients with and without adjuvant treatment.

Material and Methods

From 1960 through 1978, 79 patients with nasopharyngeal SCC were treated with irradiation at this department. Two patients lost to follow-up were excluded from the analysis. Follow-up of the other 77 patients was complete, including recorded reviews, and direct contact with patients or family members. The series comprised 60 men and 17 women, of ages ranging from 8 to 86 years (mean 46.4 years, median 50 years). The patients were staged clinically according to the UICC staging system (13) as shown in Table 1. All were M0 at first presentation. Staging procedures included physical examination, inspection of the nasopharynx using indirect, direct or fiberoptic nasopharyngoscopy, skull radiography with tomograms, chest radiography and laboratory tests. Biopsy specimens were obtained from the primary tumors. Some of the patients with positive nodes had also had resection of the node(s). Included in the analysis were both squamous cell carcinomas (which nowadays are regarded as poorly differentiated squamous cell carci-

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nomas) and more differentiated squamous cell carcinomas.

All patients were treated with irradiation; 6 MV roentgen rays, ^{60}Co gamma rays and 250 keV roentgen rays were used in 61, 12 and 4 patients, respectively. The patients treated with orthovoltage roentgen rays were included, as they received comparable doses to the primary site, and as we wanted to analyse a consecutive series of patients. Usually a conventional fractionation schedule was used with 2 Gy per day, 5 to 6 times per week. The primary tumor was in most patients treated by lateral opposed fields. Recently, however, a 3-field technique with two lateral and one anterior ports has been introduced. The radiation fields included the nasopharynx, usually with 0.5 to 1.0 cm margins. The tumor doses ranged from 4 to 90 Gy (mean 51 Gy, median 58 Gy); 23 patients received less than 50 Gy, 33 patients between 50 and 69 Gy and 21 patients more than 70 Gy. In some cases, irradiation was prematurely terminated because of chemotherapy-enhanced mucositis or refusal of the patients.

The patients with positive neck nodes were treated with involved or extended field irradiation to the neck. Patients with negative findings in the neck usually received irradiation to the upper cervical nodes; in recent years, however, they have received extended field irradiation. Nine patients with positive nodes had radical neck dissection, 8 of whom also had neck irradiation. For 42 patients, adjuvant chemotherapy was added to irradiation. Selection of patients for adjuvant chemotherapy depended on the preference of the physician. In 22 patients anti-cancer drugs were infused intra-arterially through cannulas inserted into the bilateral superficial temporal arteries. The other 20 patients received intravenous injections of one or more anti-cancer drugs. Single agent chemotherapy was used in 27 patients, and combination regimens in 15 patients. Common drugs used were bleomycin (BLM) or 5-fluorouracil.

The time to relapse was calculated from the date of diagnosis at this hospital. All patients were followed for more than 3 years or until death. Relapse was analysed for primary, cervical and distant sites. If failure subsequently developed at other sites within one month of the date of the first relapse, both were recorded as a first relapse. Local recurrence was usually documented by biopsy. In some cases, the original tumors persisted after the initial therapy; these were regarded as having relapsed one month after diagnosis. One T3N1M0 patient died of BLM induced pneumonitis. Although autopsy revealed no residual disease, she was included in the group of deaths from disease, and excluded from the analysis of site of failure.

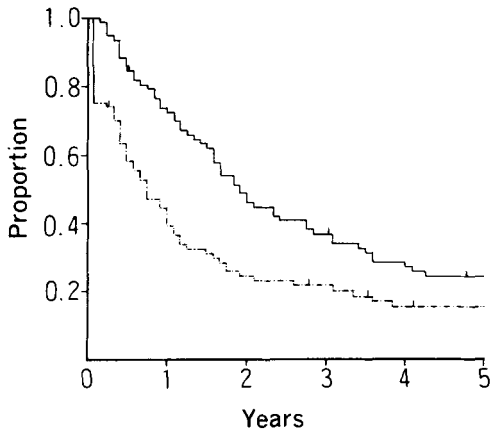

Fig. 1. Survival (——) and relapse-free survival (—·—) curves for all patients.

Table 1

T and N stages in the 77 patients with nasopharyngeal squamous cell carcinoma (all patients were M0)

T stage	N stage				Total
	N0	N1	N2	N3	
T1	5	2	3	5	15
T2	7	3	4	5	19
T3	3	5	2	8	18
T4	11	6	3	5	25
Total	26	16	12	23	77

Survival and relapse-free survival curves were calculated according to the method of KAPLAN & MEIER (14). GEHAN's modification of the generalized Wilcoxon test (7) was employed to evaluate differences in survival curves. Patients in complete remission who died of other causes were registered as alive and free of disease at the time of the last follow-up.

Results

Relapse, regardless of localization, developed in 63 (82%) of the 77 patients. Thirty-three (52%) of the 63 relapsing patients had relapse within 6 months, 73 per cent within 12 months, and 91 per cent within 24 months. Only 6 patients (9%) developed relapse first after 2 years. Five-year survival

Table 2

Site of first relapse according to T stage (per cent in parentheses)

T stage	No. at risk	Site of first relapse							Total of P	Total of C	Total of D
		P	C	D	P+C	P+D	C+D	P+C+D			
T1	15	3	5	1	3	1	0	0	7 (47)	8 (53)	2 (13)
T2	19	4	3	2	2	1	0	0	7 (37)	5 (26)	3 (16)
T3	18	5	2	1	7	0	1	1	13 (72)	11 (61)	3 (17)
T4	25	12	3	0	2	3	0	1	18 (72)	6 (24)	4 (16)
Total	77	24	13	4	14	5	1	2	45 (58)	30 (39)	12 (16)

P: Primary, C: Cervical, D: Distant.

Table 3

Site of first relapse according to N stage (per cent in parentheses)

N stage	No. at risk	Site of first relapse							Total of P	Total of C	Total of D
		P	C	D	P+C	P+D	C+D	P+C+D			
N0	26	10	4	1	1	1	0	0	12 (46)	5 (19)	2 (8)
N1	16	4	3	1	4	1	0	1	10 (63)	8 (50)	3 (19)
N2	12	2	1	2	5	1	0	0	8 (67)	6 (50)	3 (17)
N3	23	8	5	0	4	2	1	1	15 (65)	11 (48)	4 (17)
Total	77	24	13	4	14	5	1	2	45 (58)	30 (39)	12 (16)

P: Primary, C: Cervical, D: Distant.

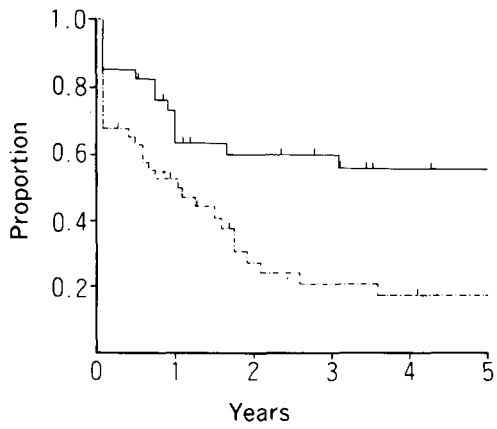

Fig. 2. Local recurrence-free survival curves for T1 + T2 (—) and T3 + T4 (–·–) groups.

and relapse-free survival for all patients were 25 and 16 per cent, respectively (Fig. 1). Three patients were successfully salvaged after relapse, and are alive and well at the time of writing.

Failures most commonly occurred at the primary sites. Local recurrence constituted the first relapse in 45 (71%) of the 63 relapsing patients, 24 of whom had local recurrence alone (Table 2). Local recurrence rates did not appear to differ between the T1 and T2 patients, or between the T3 and T4 patients. Local recurrence was more common in the T3 +T4 group than in the T1 + T2 group. Five-year local recurrence-free survival rates for the T1 + T2 group and T3 + T4 group were 56 and 17 per cent, respectively ($p<0.02$; Fig. 2). Twenty-two (35%) of the 63 relapsing patients had their first relapse at two or more sites simultaneously.

Cervical failures as first relapse were seen in 30 (48%) of the 63 relapsing patients, 13 of whom had cervical failures alone. Cervical failure rates were higher in the patients with positive nodes at first presentation (N+) than in the patients with negative nodes (N0; Table 3). The cervical failure rates did not appear to differ among the N1, N2 and N3 patients. Five-year cervical failure-free survival rates for the N0 and N+ patients were 74 and 42 per cent, respectively ($p<0.02$).

Distant metastases as a component of first relapse

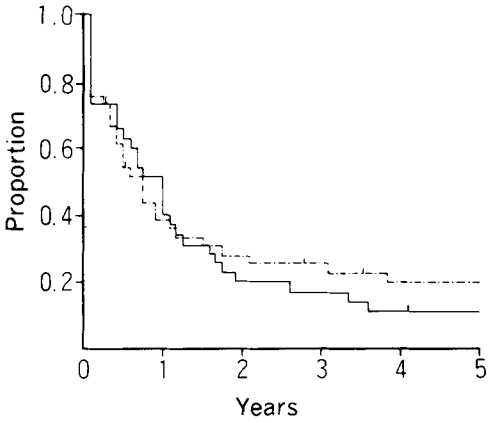

Fig. 3. Relapse-free survival curves for the patients with radiation therapy alone (——), and those with adjuvant chemotherapy (—·—).

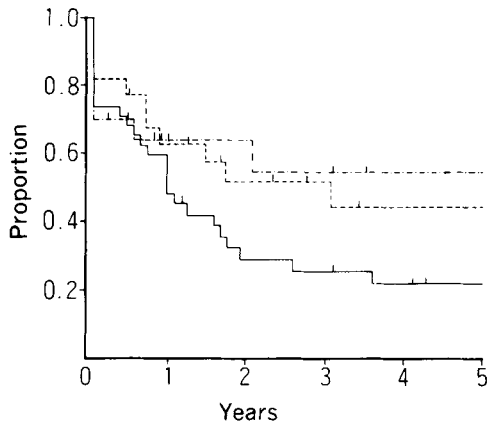

Fig. 4. Local recurrence-free survival curves for the patients with radiation therapy alone (——), those with intra-arterial adjuvant chemotherapy, (– – –), and those with intravenous adjuvant chemotherapy (—·—). The differences were not statistically significant.

were seen in 12 (19%) of the relapsing patients. Distant metastases rates did not appear to relate to the T stage (Table 2). However, the N stage seemed to have some prognostic significance for development of distant metastases (Table 3). Five-year distant metastases-free survival rates for the N0 and N+ patients were 92 and 71 per cent, respectively, but this difference was not statistically significant. Nine of the 51 relapsing patients without generalized disease at the first relapse subsequently developed distant metastases.

Five-year survival rates for the patients with irradiation alone and for the patients with irradiation and adjuvant chemotherapy were 24 and 22 per cent, respectively. Although not statistically significant, the 5-year relapse-free survival rate was higher in the patients with, than without adjuvant chemotherapy (20% versus 11%; Fig. 3). This difference was mainly attributable to the difference in local recurrence-free survival rates, being 49 and 22 per cent at 5 years, for the two groups, respectively ($p=0.2$; Fig. 4). The corresponding figures for cervical failure-free and distant metastasis-free survival rates were 59 and 79 per cent for the irradiation alone group, and 47 and 79 per cent for the adjuvant chemotherapy group, respectively, with no significant differences. The difference in local recurrence-free survival rates may be due to different distribution of T stages within the two groups; T3 and T4 cases were relatively more frequent in the irradiation alone group than in the adjuvant chemotherapy group (Table 4). Five-year local recurrence-free survival rates for the irradiation alone group and the adjuvant chemotherapy group were 47 and 61 per cent in T1 + T2 tumors, and 13 and 24 per cent in T3 + T4 tumors, respectively, with no statistically significant difference.

Table 4

Distribution of the stages according to the treatment (per cent in parentheses)

T and N stage	Irradiation alone	Adjuvant chemotherapy	Total
T1, T2	12 (34)	22 (52)	34 (44)
T3, T4	23 (66)	20 (48)	43 (56)
N0	11 (31)	15 (36)	26 (34)
N1, N2, N3	24 (69)	27 (64)	51 (66)
Total	35	42	77

Autopsy was performed in 11 patients. Distant metastases were very common at autopsy. One patient died of BLM-related pneumonitis, and had no residual disease at autopsy. The other 10 patients had residual disease: 5 in the primary site, 5 in the neck, and 9 in a distant organ or organs. Lung, liver and bone metastases were found in 8, 7, and 7 patients, respectively. Four patients had lesions only in distant organs. In 2 of these 4 patients the first relapse had occurred in the neck and the neck lesions had been successfully eradicated.

Discussion

Failure patterns for cancer of any site are important because they give clues as to efforts which should be made in order to improve control rates. The reported control rates for nasopharyngeal SCC vary among different departments and range from 15

to 62 per cent (1, 2–6, 8–10, 12, 17, 18–20, 23). One reason for this may be differences in stage distribution. Many papers report success rates in terms of 3- or 5-year survival rates (1, 2, 4, 5, 10, 12, 19, 20, 23). The relapse-free survival rate may be a more adequate measure for comparison of treatment results in nasopharyngeal SCC.

The present analysis again confirmed the importance of achieving local control in the treatment of nasopharyngeal SCC. Most of the relapsing patients had local recurrence as a component of their first relapse. The probability of local control appeared to correlate with the T stage. A higher local control rate in early lesions has also been reported in other series (3–5, 8–10, 12, 18, 19, 23).

Since 1978, we have performed computed tomography (CT) in new patients with nasopharyngeal SCC. This has shown that the primary tumors are usually more extensive than when estimated by conventional staging without CT. In 34 new patients with nasopharyngeal SCC the classification before CT was T1 in 6, T2 in 11, T3 in 9, and T4 in 8 patients. Ten (59%) of the 17 T1 + T2 patients were upstaged by the CT findings (24). From this experience, the fields used in the current study seemed to be too small in most patients. The fields for the primary tumor should usually include the sphenoid sinuses and the posterior half of the nasal cavities. Blocks for protection of the ears should not be used (17), unless boost irradiation of the posterior part of the nasopharynx is given (18).

Distant metastases are common in nasopharyngeal SCC, with bones, lungs and liver at the highest risk. In the literature, rates of distant metastases range from 3 to 39 per cent (1, 2, 3, 15, 16, 18, 19, 21, 22). Most of these figures refer to the whole follow-up period. In only a few reports has the rate of distant metastases as the first sign of relapse been analysed, and has revealed rates varying from 13 to 19 per cent (4, 6, 9). In the present analysis, distant metastases as first relapse were seen in 12 (19%) of the 63 relapsing patients. Although the chemotherapy used in this study seemed ineffective in reducing distant failure, other chemotherapeutic regimens in addition to radiation therapy may increase relapse-free survival in high risk patients.

REFERENCES

1. AMORNMARN R., PREMPREE T., SEWCHAND W. and JAIWATANA J.: Radiation management of advanced nasopharyngeal cancer. Cancer 52 (1983), 802.
2. BAKER S. R. and WOLFE R. A.: Prognostic factors of nasopharyngeal malignancy. Cancer 49 (1982), 163.
3. BEDWINEK J. M., PEREZ C. A. and KEYS D. J.: Analysis of failures after definitive irradiation for epidermoid carcinoma of the nasopharynx. Cancer 45 (1980), 2725.
4. CELLAI E., CHIAVACCI A., OLMI P. and CARCANGIU M. L.: Carcinoma of the nasopharynx. Results of radiation therapy. Acta radiol. Oncology 21 (1982), 87.
5. CHEN K. Y. and FLETCHER G. H.: Malignant tumors of the nasopharynx. Radiology 99 (1971), 165.
6. COOPER J. S., ROVE J. D. and NEWALL J.: Regional stage IV carcinoma of the nasopharynx treated by aggressive radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 9 (1983), 1737.
7. GEHAN E. A.: A generalized Wilcoxon test for comparing arbitrarily signle-censored samples. Biometrika 52 (1965), 203.
8. HO J. H. C.: An epidermiologic and clinical study of nasopharyngeal carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 4 (1978), 183.
9. HOPPE R. T., GOFFINET D. R. and BAGSHAW M. A.: Carcinoma of the nasopharynx. Eighteen years' experience with megavoltage radiation therapy. Cancer 37 (1976), 2605.
10. HSIEH T.: Clinical and statistical studies of nasopharyngeal cancers in Taiwan. Proc. Sec. Asia-Oceania Cong. Otorhinolaryn. Nov. 1971.
11. HUANG S. H.: Nasopharyngeal cancer. A review of 1605 patients treated radically with Cobalt 60. Int. J. Radiat. Oncol. Biol. Phys. 6 (1980), 401.
12. — and CHU G. L.: Nasopharyngeal cancer. Study II. Int. J. Radiat. Oncol. Phys. 7 (1981), 713.
13. International Union against Cancer: UICC, TNM classification of malignant tumours. Third edition, p. 27, Geneva 1978.
14. KAPLAN E. L. and MEIER P.: Nonparametric estimation from incomplete observations. J. Amer. Statist. Ass. 53 (1958), 457,
15. KHOR T. J., TAN B. C., CHUA E. J. and CHIA K. B.: Distant metastases in nasopharyngeal carcinoma. Clin. Radiol. 29 (1978), 27.
16. LEWLEY M.: Nasopharyngeal carcinoma. An account of the cranial nerve lesions found in 185 cases. Aust. N. Z. J. Surg. 25 (1956), 170.
17. MARKS J. E., BEDWINEK J. M., LEE F., PURDY J. A. and PEREZ C. A.: Dose-response analysis for nasopharyngeal carcinoma. An historical perspective. Cancer 50 (1982), 1042.
18. MESIC J. B., FLETCHER G. H. and GOEPFERT H.: Megavoltage irradiation of epithelial tumors of the nasopharynx. Int. J. Radiat. Oncol. Biol. Phys. 7 (1981), 447.
19. MOENCH H. C. and PHILLIPS T. L.: Carcinoma of the nasopharynx. Review of 146 patients with emphasis on radiation dose and time factors. Amer. J. Surg. 124 (1972), 515.
20. PETROVICH Z., COX J. D., ROSWIT B. et coll.: Advanced carcinoma of the nasopharynx. A clinical study of 274 patients. Radiology 144 (1982), 905.

21. PROBERT J. C., THOMPSON R. W. and BAGSHAW M. A.: Patterns of spread of distant metastases in head and neck cancer. Cancer 33 (1974), 127.
22. RUBENFELD S., KAPLAN G. and HOLDER A. A.: Distant metastases from head and neck cancer. Amer. J. Roentgenol. 87 (1962), 441.
23. WANG C. C.: Treatment of malignant tumors of the nasopharynx. Otolaryng. Clin. N. Amer. 13 (1980), 477.
24. YAMASHITA S., KONDO M. and HASHIMOTO S.: Conversion of T-stages of nasopharyngeal carcinoma by computed tomography. Int. J. Radiat. Oncol. Biol. Phys. 11 (1985), 1017.