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PROGNOSTIC FACTORS IN PATIENTS WITH NASOPHARYNGEAL CARCINOMA

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From 1971 to 1985 a total of 122 patients with non-distant metastatic nasopharyngeal carcinoma were treated at the Norwegian Radium Hospital with radiation doses that increased from 50 Gy (at 2 Gy/fractions) to 70 Gy (at 2 Gy/fractions) during the treatment period. Possible relationship between the increase in dose and survival time was investigated. The median cancer-specific survival time was 50 months, and the median crude survival time 38 months. No correlation was found between radiation dose and survival time. In a multivariate analysis histology was found to be the most important prognostic factor for survival with a relative risk of death from cancer of 3.4 and 3.2 for non-keratinizing carcinoma and squamous cell carcinoma respectively compared with undifferentiated carcinoma. When assessed in terms of N category the relative death risk for N2/N3 was 2.1 compared to N0/N1.

The incidence of nasopharyngeal carcinoma (NPC) in Europe and the USA is very low compared with some parts of South-East Asia and Africa. The difference in incidence and the ethnic disparity between the patient population in these regions may well mean that they are not comparable. A further discrepancy is the fact that the 5-year survival rate varies from 17% to 89% for patients treated with radiotherapy (1, 2). The success of the treatment seems to depend, among other things, on disease stage, sex and histological diagnosis. However, the histological classifications have not always been optimal; different classification systems have been used, and hence the findings are not always consistent (3). Radiation therapy is the treatment of choice, but optimal field size, dose and fractionation regimens are still a matter of debate (3, 4). In some series, for example, patients with negative neck nodes received no prophylactic neck irradiation (3, 4). In others the total dose, number of fractions per week, and dose per fraction have varied within the same patient population (3). Various boost techniques have been used: regular boost with reduced portals after primary treatment (5), concomitant boost (6) and intra-cavitary boost (7, 8). Accelerated hyper-fractionated radiation therapy (twice a day) seems to have improved the local control rate compared with conventional fractionation (once a day) (9), but randomized clinical trials will have to be carried out to confirm this theory. In several non-randomized trials strong correlations have been found between treatment dose and survival time (4, 5). At the Norwegian Radium Hospital (NRH) the radiation dose was increased from 50 Gy (2 Gy per fraction) to 60 Gy (2 Gy per fraction) and finally to 70 Gy (2 Gy per fraction) between 1970 and 1985. During this period one fraction was delivered per day, five days a week. The present study was undertaken to investigate whether these radiation doses influenced the survival time.

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Material and Methods

From 1971 to 1985, 122 patients with NPC without distant metastases were treated with radiotherapy at NRH,

and none were lost to follow-up. Ninety of the patients were men and 32 women. The mean age was 59 years, with a range of 11 to 83 years. All patients were staged retrospectively according to UICC TNM classification (1989) based on recorded data from physical examination, panendoscopy, skull x-ray, chest x-ray and/or computed tomography (CT) scan.

The tumors were classified histologically on the basis of morphological criteria proposed by WHO (10). The histological diagnoses were revised and classified independently and blindly by two pathologists who had no information of the clinical findings or the outcome of the treatments (11). Where opinions differed, the slides were evaluated jointly to obtain consensus. The routine was also to examine the paraffin-embedded material by immunohistochemistry techniques. A large group of patients were found to have non-keratinizing (NK) carcinoma (39%), and 31% had undifferentiated carcinoma while 27 patients had squamous cell carcinoma (Table 1). Ten tumors were classified as adenocarcinoma, adenoid cystic carcinoma, or unclassified carcinoma. In the final survival analysis the patients were divided into 3 major groups: Keratinizing squamous cell carcinoma (22%), NK carcinoma (39%) and undifferentiated carcinoma which included adenocarcinoma, adenoid cystic carcinoma and unclassified carcinoma (39%). The adenocarcinomas, adenoid cystic carcinomas and unclassified carcinomas were placed in the latter group on the basis of the univariate survival analysis.

Opposite bilateral portals were used to irradiate both the primary tumor and upper neck. The lower neck, including the supraclavicular and infraclavicular regions, were treated with anterior-posterior irradiation in most patients. One patient was treated by opposite bilateral portals, and one by a unilateral field. The necks of N0 patients were treated prophylactically with a dose of 50 Gy, while the positive necks were treated with doses of between 50 and 70 Gy. The spinal cord was shielded after administration of 40 Gy over 4 weeks and the posterior cervical triangles were boosted with electrons to protect the underlying spinal cord. The primary tumor and positive neck nodes were boosted to the maximal dose in the given treatment period. Most of the patients were treated with a conventional treatment schedule of 2 Gy per fraction, 5 days a week.

In the survival analysis both crude survival and cancer specific survival were calculated. Median survival was calculated according to the life-table analysis and group differences were tested by a log-rank test (12). A stepwise multiple regression analysis (Cox analysis) was used to measure the prognostic association to the various factors (13, 14). Results are reported as relative risks (RR), computed from the relative hazard estimates. In the regression analysis age is treated as a continuous variable. In Tables 5 and 6, estimates are calculated for a 10-year interval.

Results

The distribution of clinical stage according to T and N categories are shown in Table 2. The largest patient group had a T4 tumor (43%). Thirty-eight percent were node negative and 18% had N3 disease. The radiation doses administered to the primary tumor are shown in Table 3. In 1971–1975, all patients received 60 Gy or less. In 1981–1987, however, 33 out of 35 patients received more than 60 Gy. The doses to the neck follow a similar pattern except that the change in dose distribution occurred primarily between the periods 1971–1975 and 1976–1980.

The univariate cancer specific and crude survival times are shown in Table 4. The median cancer specific survival time was 50 months (Table 4) (Fig. 1), while the median crude survival time was 38 months (Fig. 2). Patients with undifferentiated carcinomas lived statistically significantly longer than patients with other diagnoses (Fig. 3). Similar findings were found for N0/N1 versus N2/N3 disease (Fig. 4) and there was a tendency for patients with T1/T2 to live longer than T3/T4 patients ($p = 0.09$). Younger patients had longer survival time than older and women tended to live longer than men. Similar results were found in the crude survival analysis. The most important factors for both cancer specific death and crude death were

Table 1

Histopathological diagnosis

	n
Poorly diff. squamous cell ca.	18
Moderately diff. squamous cell ca.	8
Well diff. squamous cell ca.	1
Non-keratinizing ca.	47
Undiff. ca.	38
Other types (adenoca., adenoid cystic ca, and unclassified ca.)	10

Table 2

Nasopharyngeal carcinoma, classified according to T and N categories. Numbers of patients

T category	N category				
	N0	N1	N2	N3	Total
T1	4	5	11	6	26
T2	9	2	10	3	24
T3	6	—	9	5	20
T4	27	3	14	8	52
Total	46	10	44	22	122

Table 3

Radiotherapy to the primary tumor and neck nodes for 122 patients with nasopharyngeal carcinoma. Dose distribution according to treatment period

	1971–1975		1976–1980		1981–1987		Total (%)	
Gy	Primary	Neck nodes	Primary	Neck nodes	Primary	Neck nodes	Primary	Neck nodes
0		1	—	2	—	1	—	4 (3)
⩽50	27	26	5	12	—	19	32 (26)	57 (47)
51–60	21	21	11	20	2	11	34 (28)	52 (43)
>60	—	—	23	5	33	4	56 (46)	9 (7)
Total	48	48	39	39	35	35	122	122

Table 4

Univariate cancer specific and crude survival analysis

Variable	No. of patients	Median survival in months (% at 5 years)	
		Cancer specific	Crude
Total population	122	50 (45)	38 (37)
Radiotherapy			
⩽50 Gy	32	56 (49)	44 (44)
51–60 Gy	34	55 (47)	43 (35)
>60 Gy	56	44 (42)	32 (34)
Histology			
Non-keratinizing ca.	47	37 (29)	26 (23)
Squamous cell ca.	27	22 (35)	22 (31)
Undiff. ca/other	48	a (66)	88 (54)
Stage			
T1–T2	50	88 (44)	53 (30)
T3–T4	72	40 (31)	32* (16)
N0–N1	56	68 (44)	47 (29)
N2–N3	66	32** (30)	24* (17)
Sex			
Men	90	43 (32)	35 (34)
Women	32	95 (50)	53 (46)
Age			
1–49	25	113 (47)	108 (45)
50–69	66	59 (38)	48 (45)
⩾70	31	17** (24)	13** (3)

a 55% survival at this point
* $p < 0.05$
** $p < 0.01$

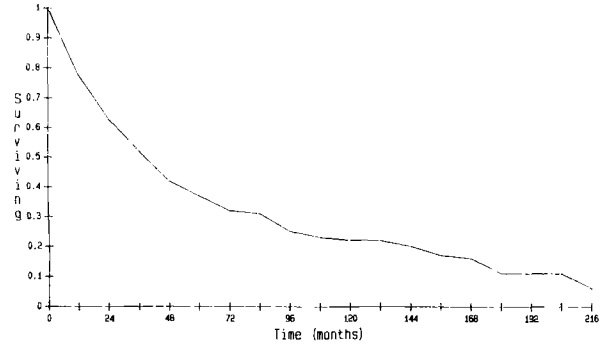

Fig. 1. Cancer specific survival in patients treated for nasopharyngeal carcinoma.

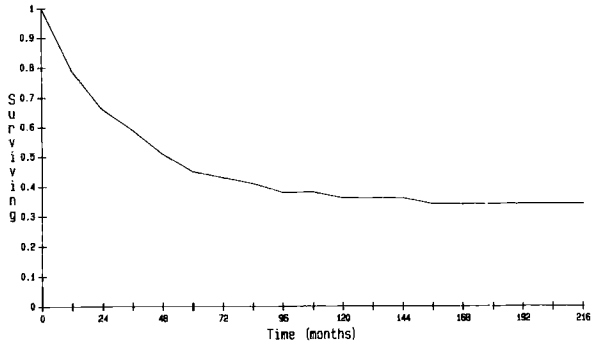

Fig. 2. Crude survival in patients treated for nasopharyngeal carcinoma.

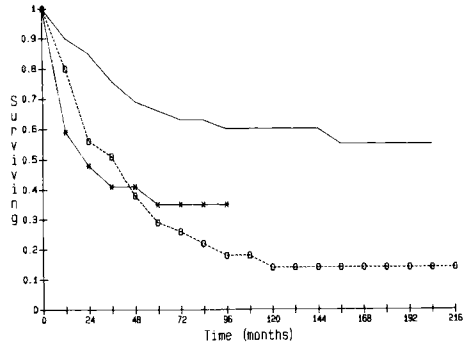

Fig. 3. Cancer specific survival in relation to histological classification. — undiff. ca.; --○-- non-keratinizing ca.; – × – squamous cell ca.

histology, disease stage and age (Table 5). The relative risk of death was somewhat lower for patients who received 60 Gy than for patients treated with higher radiation doses, but the difference was not statistically significant.

In a stepwise multiple regression analysis for cancer-specific death the adjusted relative risk of death for NK carcinoma and squamous cell carcinoma were 3.38 and 3.21 respectively (Table 6). Patients with N2/N3 disease had an adjusted relative risk of death of 2.06. In a similar analysis of crude death (Table 6), age had a relative risk of 1.38 per 10 year, followed by the two histology variables and node diseases (N2/N3).

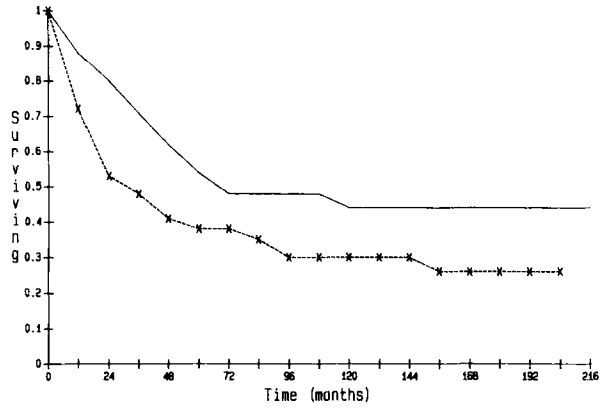

Fig. 4. Cancer specific survival in relation to N category. — N0–N1; ---×--- N2–N3.

Discussion

In the present study no dose–response relation was found between radiation doses of 50 to 70 Gy and survival time. The 5-year cancer-specific survival rate varied from 42% to 49% in the different dose groups (Table 4). This result is somewhat surprising as a relation between dose and survival time has been reported in some earlier studies (4, 5, 15). In one of these studies, (15), however, the results may have been biased by including also patients with improperly designed fields in the low-dose group. All these studies, including our own, were retrospective and non-randomized, which severely limits the possibility to draw any conclusions. Changes may thus have occurred at the same time concerning other variables than the radiation dose; the field size may for instance have been increased in addition to the radiation dose. This was the case in one of the mentioned studies (4), which reported improved local recurrence-free survival time.

Unfortunately, we do not have high quality data on loco-regional relapse, and therefore cannot compare this variable with other studies. In the present study CT scans were more often used in the 80s than in the 70s, which should have improved the design of the radiotherapy fields. However, no obvious differences in survival were seen between the different time periods. In another reported study no differences were found in local recurrence rate between patients planned for radiotherapy with and without CT/MI scan (16). Due to the follow-up procedures in the 70s and early 80s, data on primary tumor response and pattern of failure were not available in the present study.

In some earlier studies different histological cell types may have been included such as lymphomas. Another factor influencing reported results can be selection of patients with especially good prognosis. The present patient population represented more than two-thirds of the diagnosed NPC without distant metastases in Norway during the given time period, and should be fairly representative of the Norwegian population. The reported 5-year survival

Table 5

Univariate estimates of relative risk (RR) with 95% confidence interval (CI)

	Crude death		Cancer death	
	RR*	(95% CI)	RR	(95% CI)
Sex				
Women	0.68	(0.38, 1.24)	0.76	(0.47, 1.23)
Men	(1.00)	(Ref)	(1.00)	(Ref)
Age (10 year interval)	1.19	(0.96, 1.46)	1.39	(1.16, 1.67)
Radiotherapy				
≤51 Gy	0.72	(0.37, 1.38)	1.13	(0.64, 2.00)
51–60 Gy	0.79	(0.41, 1.51)	1.19	(0.66, 2.14)
>60 Gy	(1.00)	(Ref)	(1.00)	(Ref)
Histology				
Non-keratinizing ca.	2.94	(1.57, 5.47)	2.12	(1.28, 3.51)
Squamous cell ca.	3.01	(1.41, 6.43)	2.18	(1.18, 4.02)
Undifferentiated ca.	(1.00)	(Ref)	(1.00)	(Ref)
Stage				
T3–T4	1.12	(0.66, 1.88)	1.21	(0.78, 1.87)
T1–T2	(1.00)	(Ref)	(1.00)	(Ref)
N2–N3	2.17	(1.30, 3.62)	1.72	(1.13, 2.63)
N0–N1	(1.00)	(Ref)	(1.00)	(Ref)

* Equivalent to relative hazard rates.

Table 6

Stepwise multiple Cox's regression analysis of statistically significant variables in sequence adjusted for sex, age, treatment dose and T category

Variable	Cancer death		Crude death	
	RR*	(95% CI†)	RR	(95% CI)
Age (10 years interval)	—	—	1.38	(1.15, 1.64)
Non-keratinizing ca.	3.38	(1.87, 6.11)	2.32	(1.43, 3.77)
Squamous cell ca.	3.21	(1.62, 6.36)	2.47	(1.40, 4.37)
N2–N3	2.06	(1.26, 3.39)	1.68	(1.12, 2.53)

* Relative risk
† Confidence interval

rates for patients with NPC varies in the literature from 17 to 89% (1, 2, 8, 17, 18). Differences in survival may be explained by biological, cultural and socioeconomic differences, by age at onset of disease, and by staging and selection biases. The present analysis was made on patients without distant metastases since we wished to evaluate the curvative potential of different radiation doses. The survival rate in our patient population was similar to or better than most other series (1, 2), with 5-year and 10-year survival rates of 45% and 36% respectively.

Patients with squamous cell carcinoma and non-keratinizing carcinoma had more than 3 times the risk of dying compared with patients with undifferentiated NPC. A nodal status of N2–N3 was also a statistically significant predictor of survival. Related results were found in another study, where distant metastases after primary radiotherapy were more strongly related to initial N category than to initial T category (2). These findings support the hypothesis that N category is a better predictor of survival than T category.

Deaths from causes other than cancer due to high radiation dose in the given sample may have increased the non-cancer mortality. However, on examining the death certificates we found no systematic relation between late radiation damage to the scull and/or brain and specific causes of death.

In the present study we investigated some well-known prognostic factors. Somewhat surprising was the finding that an increase of the radiation dose did not improve survival. This indicates that some patients may have been overtreated and raises the question of whether or not all patients with NPC should be treated with radiation doses of 66–70 Gy. A better selection of patients based on prognostic factors and a detailed assessment of response after completion of therapy by means of fiberscope, biopsies and CT or MR scan are needed. Recent studies have shown that non-complete responders may benefit from the boost technique (7), and other studies have shown that accelerated hyperfractionated regimens (8) and concomitant boost radiotherapy may improve the survival time (6). Also the combination of radiotherapy and adjuvant chemotherapy needs further exploration. Multicenter randomized studies might provide more reliable guidelines for the treatment of these patients.

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