Nasopharyngeal carcinoma—presenting symptoms and duration before diagnosis

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This is a retrospective analysis of 4768 patients with undifferentiated or non-keratinising carcinoma of the nasopharynx who were treated during 1 January 1976 to 31 December 1985. The mean duration of symptoms before diagnosis was 8 months (range, 1-36 months for 95% of patients). A significant association between the duration of symptoms and the presenting stage was observed (P<0.001); 58% and 39% of stage I and stage V patients, respectively, reported as having had symptoms for less than 6 months. Of the later presenters (those having had symptoms for 6 months or longer), 89% were given a full course of radical megavoltage radiotherapy, but 6% were too advanced for any irradiation attempt. Consequently, the 10-year actuarial disease-specific survival was significantly higher among the early presenters: 48% versus 42% (P<0.001). The importance of early detection is emphasised.

Introduction

Throughout the past decade, nasopharyngeal carcinoma (NPC) has been the third most common cancer and the third most common cause of cancer death in the male population of Hong Kong. Nasopharyngeal carcinoma has a tendency to affect the relatively young population more than most other cancers; the loss of working life due to NPC is substantial.[1]

The extent of disease at diagnosis of NPC is the most important prognostic factor.[2-7] While those with a tumour entirely confined within the nasopharynx (stage I according to Ho's classification)[8] can achieve a 5-year actuarial disease-specific survival of 81%, the median survival for those with distant dissemination (stage V) is only 5 months (Fig 1). Unfortunately, the nasopharynx is not easily visualised and requires the use of fibroscopy, or a mirror examination with or without general anaesthesia. Moreover, patients usually have minimal symptoms before the tumour extends beyond the primary site. This disease is often managed solely by radiotherapists and information about the disease from general textbooks is scant due to its rarity in the West. Consequently, doctors from other specialties (except otolaryngologists) are often unfamiliar with the natural course of NPC. It is not surprising therefore that very few patients present with Stage I disease.[9]

The purpose of this study was to review the presenting features of NPC and the detrimental effect of a delay in presentation on the final outcome.

Subjects and methods

Patient characteristics

We studied 5020 patients with undifferentiated or non-keratinising carcinoma of the nasopharynx who were primarily treated at the Queen Elizabeth Hospital during 1 January 1976 to 31 December 1985. Excluding the 252 (5.0%) patients who failed to give a clear history of symptoms and their duration, the present study concentrated on the remaining 4768 patients. The male to female ratio was 2.8 to 1.0, and their ages ranged

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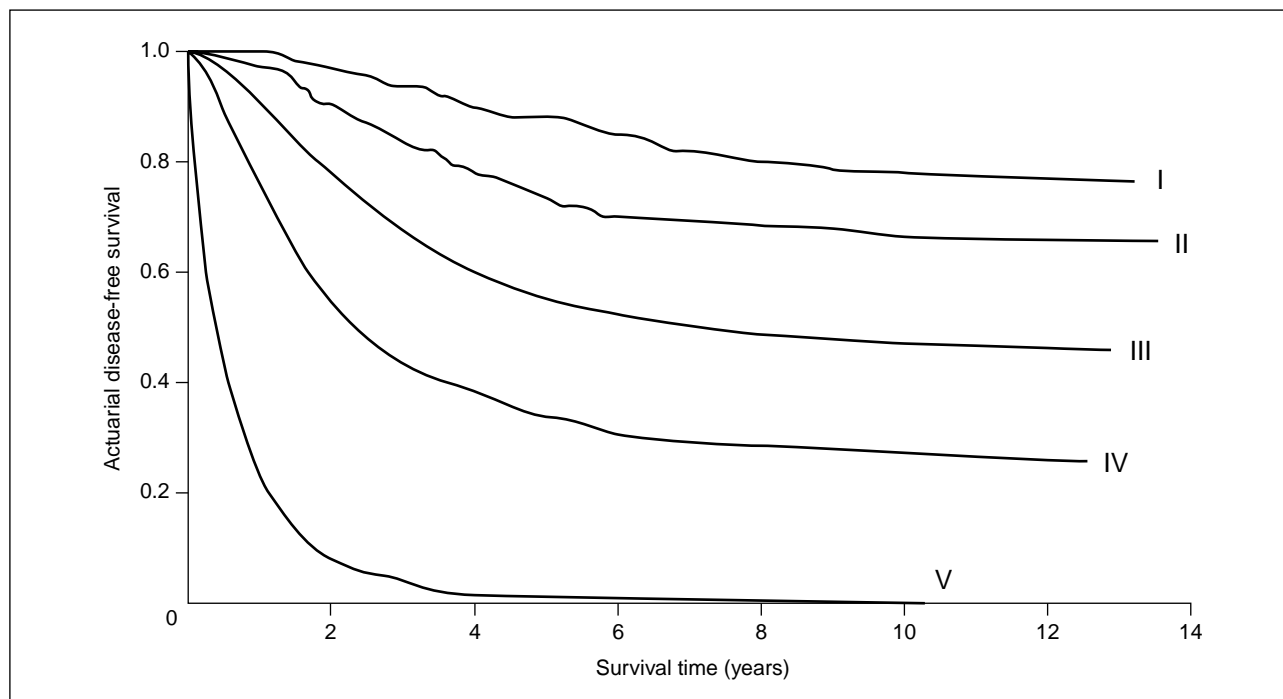SCK Law, FRCR, FHKAM (Radiology)
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Results are based on a series of 5020 patients with undifferentiated or nonkeratinising carcinoma of the nasopharynx treated at the Queen Elizabeth Hospital during 1976-1985

Fig 1. Actuarial disease-specific survival for patients with different presenting stage categories

from 10 to 88 years (median, 48 years). Ninety-one percent of patients had been regularly followed up until death or the present time of analysis.

Clinical staging

All patients were staged by anterior rhinoscopy, indirect nasopharyngoscopy, and radiography of the chest and nasopharyngeal regions using the special views recommended by Ho.[10] Computed tomography was only done in 689 (14.5%) patients, as this method of investigation was not available until late 1980. Direct fibroscopy as a method of examination of the upper airway was gradually implemented after 1982.

Treatment

The general policy was to treat as many patients as possible with radical radiotherapy. The radiation techniques and dosage schemes have been described in detail by Ho.[11] Basically, all potential sites of local infiltration were irradiated to a total dose of 65 Gy equivalent.

Only 4313 (90.5%) of the patients in the present series had a complete course of megavoltage radiotherapy. The remainder included patients who had distant metastases or extensive loco-regional infiltration: in these conditions, radical treatment was not feasible technically. Indeed, 240 (5.0%) of the patients were too ill for any form of local irradiation to be performed.

Adjunctive chemotherapy was given to 416 (8.7%) of the patients who were at an advanced stage of disease or who had a poor response to primary radiotherapy. Various cytotoxic drugs (including cisplatin, 5-fluorouracil, cyclophosphamide, methotrexate, and bleomycin) had been given. Neck dissection was done in 18 patients who had residual or recurrent lymph nodes, and lobectomy was performed in seven patients who had solitary lung metastasis.

Statistical methods

Five different aspects were studied: (1) The presenting symptoms and signs were summarised, and the pattern of the symptom duration was studied. (2) Possible host factors affecting the symptom duration were analysed with contingency tables and the Chi squared test. (3) The independent significance of the symptom duration on the presenting stage was assessed; patients were grouped into early (stages I-II) and advanced (stages III-V) stage categories. Logistic regression was applied to test the association, following adjustment for other covariates. (4) The correlation between symptom duration and subsequent radiotherapy was analysed with contingency tables and Chi squared test. (5) The effect of symptom duration on the final outcome in terms of disease-specific deaths was studied. Actuarial incidences (measured from the date of diagnosis) were calculated by the Kaplan-Meier method,[12]

Table 1. Presenting symptoms and their frequencies (n=4768)

Symptom	Number of patients		
	Only symptom	First symptom*	Total No. presenting with symptom
	No. (%)	No. (%)	No. (%)
Neck mass	37 (0.8)	1777 (37.3)	3612 (75.8)
Nasal (discharge, bleeding, obstruction)	65 (1.4)	1687 (35.4)	3501 (73.4)
Aural (tinnitus, impairment of hearing)	54 (1.1)	912 (19.1)	2975 (62.4)
Headache	13 (0.3)	175 (3.7)	1657 (34.8)
Ophthalmic (diplopia, squint)	4 (0.1)	48 (1.0)	512 (10.7)
Facial numbness	3 (0.1)	22 (0.5)	361 (7.6)
Weight loss	0	1	329 (6.9)
Trismus	2	2	141 (3.0)
Slurring of speech	0	3 (0.1)	114 (2.4)
Others due to metastatic deposits	0	12 (0.3)	57 (1.2)
Skin lesions due to dermatomyositis	4 (0.1)	6 (0.1)	42 (0.9)

*In patients presenting with multiple symptoms

and the differences were compared using the log-rank test.[13] The independent significance of the symptom-duration was further analysed by the Cox regression model.[14]

Results

Presenting features and duration

While 3903 (81.9%) of the patients presented with multiple symptoms, 851 (17.8%) reported one symptom; the remainder were asymptomatic. Forty percent of patients had no external signs. The frequency of different presenting symptoms and signs are listed in Tables 1 and 2, respectively. The painless enlargement of the upper cervical lymph node(s) was the most common presenting feature. Gross lymphatic spread at the time of diagnosis was present in 3550 (74.5%) of the patients, and of these 1788 (50.4%) had bilateral involvement. Of the whole series, 2585 (54.2%) had no physical signs other than nodal (unilateral or bilateral) enlargement.

Approximately three quarters of the patients complained of nasal symptoms; however, there was no obvious abnormality found from a general physical examination. Approximately 20% of patients presented with otological symptoms but by the time of diagnosis 62.4% were affected and 5.0% had a gross impairment of hearing. Headache and/or symptoms of cranial nerve dysfunction were rarely the first reported complaint, but 20.0% of patients eventually developed cranial or cervical sympathetic nerve palsy. Figure 2 shows the frequency of nerve involvement; the fifth and the sixth nerve were the most frequently involved (frequencies of 12.5% and 10.5% respectively).

The mean symptom duration before the establishment of a diagnosis was 8 months, with a wide range of 1 to 36 months for 95% of the series (Fig 3). For convenience, patients were divided into two groups for further analysis: a short symptom duration group of 2354 (49%) patients who had no symptoms, or had had symptoms for less than 6 months, and a long symp-

Table 2. Physical signs at the time of diagnosis and their frequencies (n=4768)

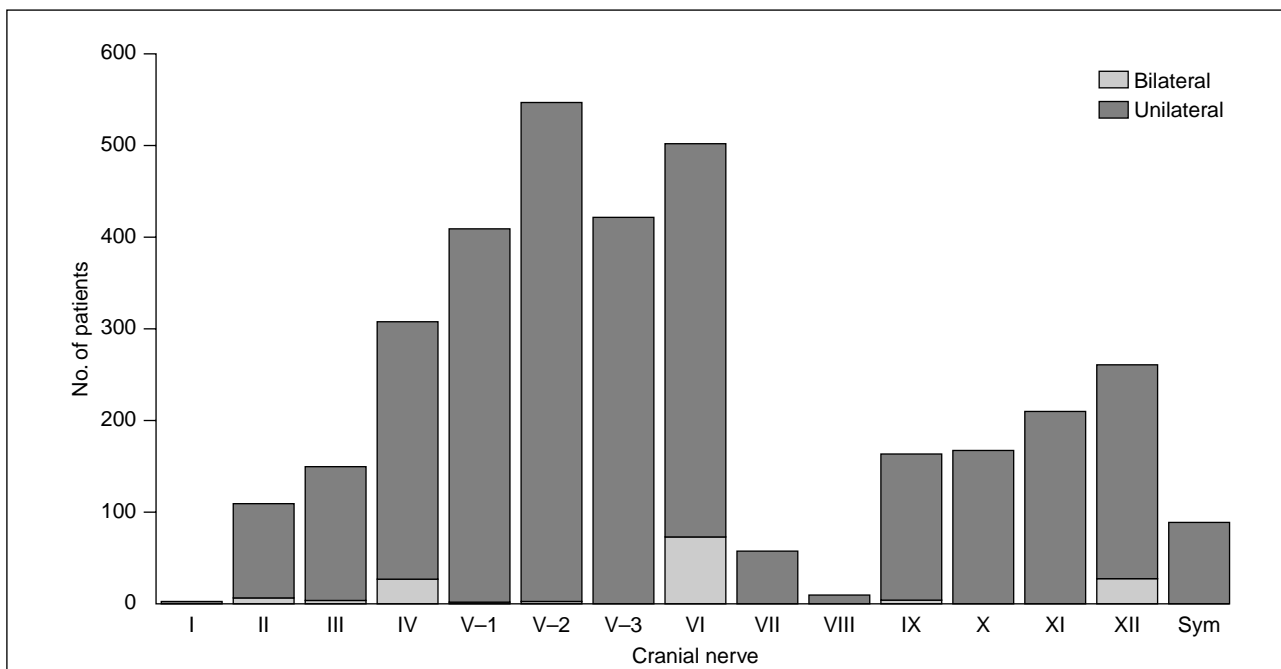| Physical sign	Only sign	One of multiple signs	Total No. at diagnosis
	No. (%)	No. (%)	No. (%)
Enlarged neck node(s)	2594 (54.4)	956 (20.1)	3550 (74.5)
Cranial nerve palsy	203 (4.3)	749 (15.7)	952 (20.0)
Deafness	51 (1.1)	186 (3.9)	237 (5.0)
Trismus	3 (0.1)	70 (1.5)	73 (1.5)
Proptosis	1	15 (0.3)	16 (0.3)
Metastases	0	122 (2.6)	122 (2.6)
Dermatomyositis	17 (0.4)	17 (0.4)	34 (0.7)

Fig 2. Involvement of different cranial nerves at diagnosis (n=4768)

tom duration group of 2414 (51%) patients who had had symptoms for 6 months or longer. These groups are hereafter referred to as early and late presenters, respectively.

Factors affecting duration of symptoms
A larger proportion of the male patients had had symptoms for 6 months or less when compared with the females (51% versus 46%; P=0.003). There was also a trend towards an earlier presentation in the younger patients. The proportion of early presenters in patients aged below 40, 40 to 60, and above 60 years were 52%, 49% and 47%, respectively; the difference was just short of statistical significance (P=0.066). Patients treated in the latter half of the study period presented significantly earlier: the proportion of early presenters was 54% during the years 1981 to 1985 compared with 44% during the years 1976 to 1980 (P<0.001). The mean symptom duration was also shorter (7.4 months compared with 8.8 months).
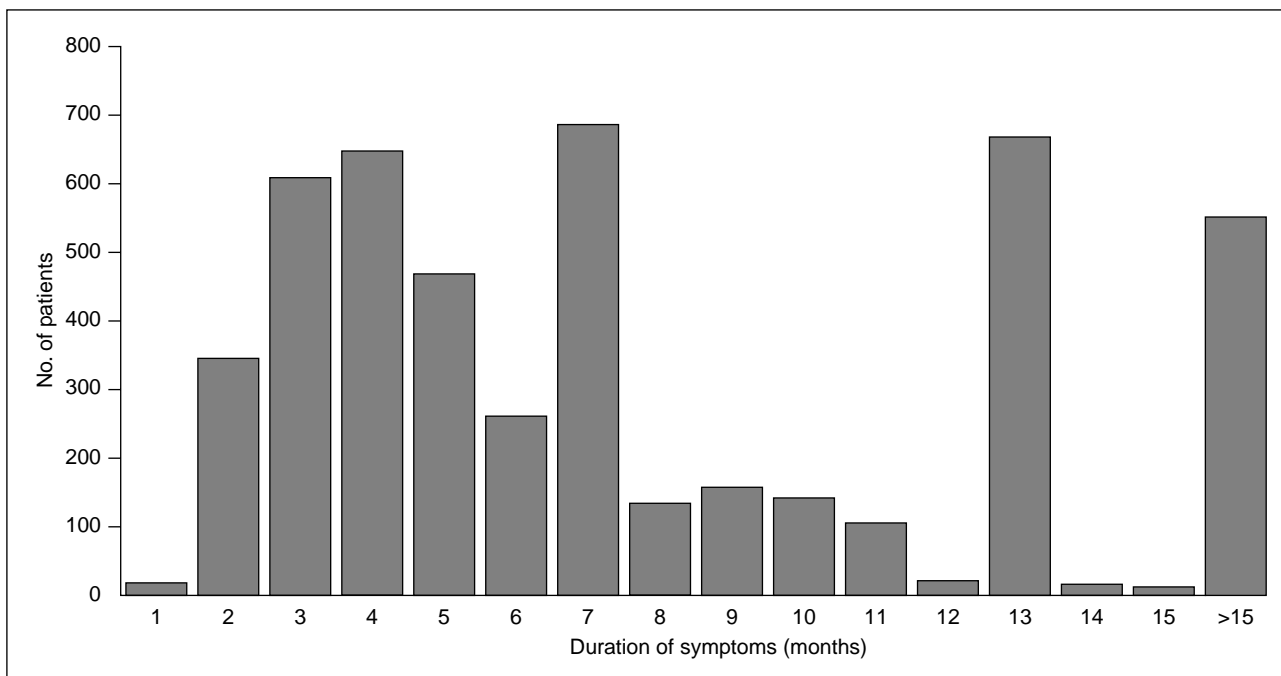

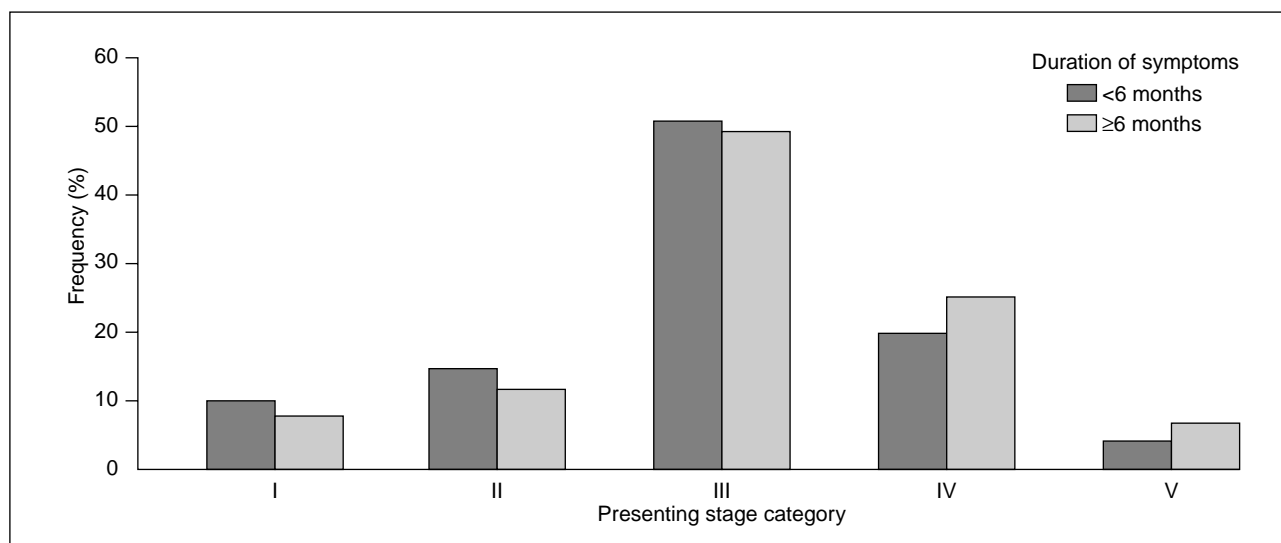**Fig 3. Distribution of duration of symptom(s)**

Fig 4. Relationship between symptom duration and presenting stage category

Factors affecting presenting stage and radiotherapy
Figure 4 shows the different distributions of stage category for the two groups. While 58% of stage I cases had had symptoms for less than 6 months, only 39% of stage V patients were early presenters (P<0.001). Logistic regression (incorporating age, sex, and treatment era as covariates) showed that symptom duration was a significant factor associated with stage category (Table 3); the odds ratio for presenting with Stage I-II disease was 0.981 per month's delay in diagnosis (P<0.001). Consequently, the pattern of radiotherapy was different in the two groups (P=0.001). A lower proportion of late presenters had a full course of radical megavoltage radiotherapy (89% versus 92%), but more of them were too advanced for any radiotherapy attempt (6% versus 4%).

Impact on final outcome
The 10-year actuarial disease-specific survival was significantly higher in early presenters (48% versus 42%; P<0.001) [Fig 5]. Univariate analysis showed that the symptom duration was a significant prognostic factor that affected the risk of disease-specific deaths: the hazard ratio was 1.011 per month; 95% confidence interval = 1.007-1.016 per month (P<0.001). Multivariate analysis showed that the most significant prognostic factors were age, sex, treatment era, presenting stage

and completeness of radiotherapy (Table 4). When adjusted for these factors, the impact of symptom duration failed to show statistical significance (P=0.14).

Discussion

The presenting stage is one of the most important prognostic factors affecting the survival for patients with NPC (Fig 1). There are marked differences in the incidence of treatment failure and there is often a need for salvage/supportive treatment. The impacts due to the subsequent loss of working life and the cost of health care are substantial.

One of the significant factors associated with the presenting stage for undifferentiated or non-keratinising carcinoma (which accounted for 99.7% of the NPC cases in Hong Kong in this study) was the duration of symptom(s) before the establishment of the diagnosis (Fig 4 and Table 3). Logistic regression showed that the odds of presenting with Stage I-II diseases decreased by 2% for each month's delay in diagnosis.

An untreated tumour leads to extensive damage and an increased chance of dissemination; it was thus not surprising that a larger proportion of the late presenters was too ill for any local treatment (6% compared

Table 3. Logistic regression analysis of the association between stage category (I-II versus III-V) and various factors

Factor	Odds ratio	95% confidence interval	P value
Age (years)	0.991	0.986-0.997	0.002
Sex (male, female)	0.819	0.760-0.883	<0.001
Treatment era (1981-85, 1976-80)	0.971	0.906-1.040	0.401
Symptom duration (months)	0.981	0.972-0.990	<0.001
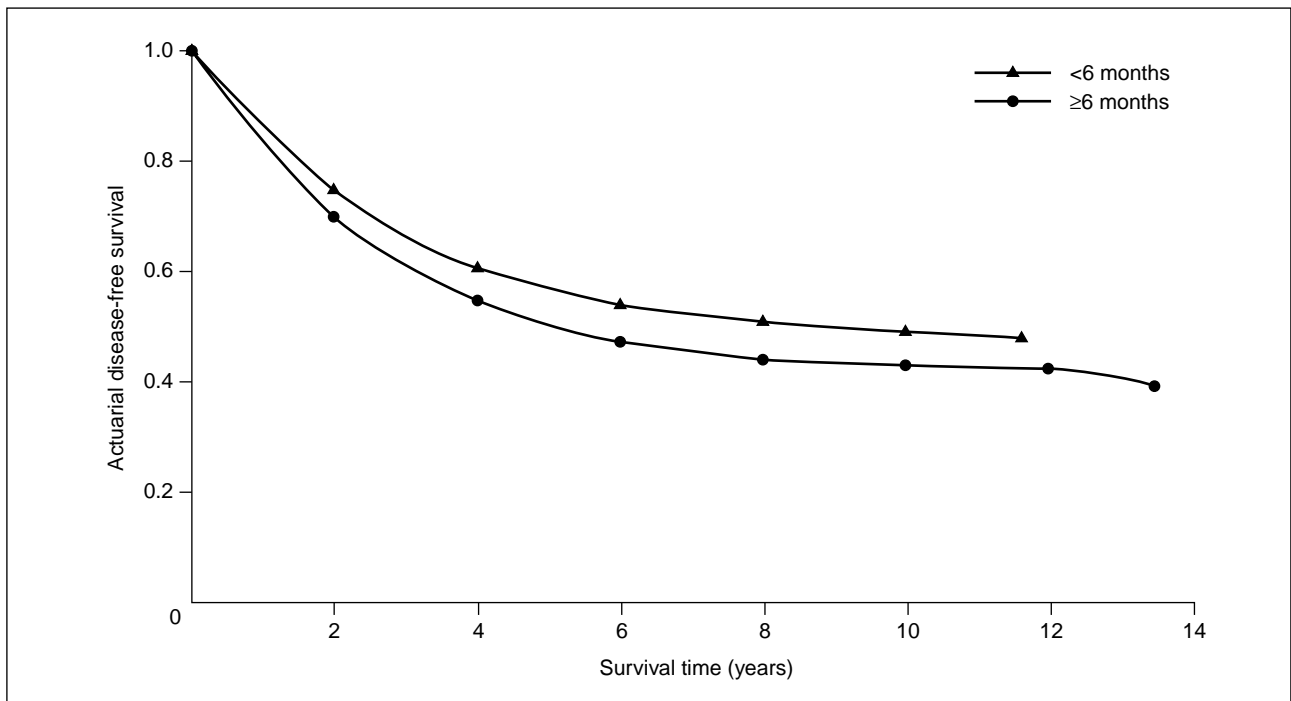
*Early and late presenters reported symptom duration of less than 6 months, and 6 months or longer, respectively

Fig 5. Actuarial disease-specific survival for early and late presenters[*]

with 4% for the early presenters). In addition, a smaller proportion of the late presenters received a full course of radical radiotherapy by megavoltage photons (89% versus 92%). The adverse effect on these two most important prognostic factors was reflected by the significantly lower 10-year actuarial disease-specific survival among the late presenters (42% versus 48%; P<0.001) [Fig 5]. The symptom duration per se, however, was not an independent prognostic factor according to the analysis by the Cox regression model (P=0.14) [Table 4].

More than half of the patients treated during this study had had symptoms for 6 months or longer before referral to radiotherapy departments (Fig. 3); there was nevertheless a sign of improvement thereafter. Despite there being a significantly larger proportion

of early presenters in the latter era studied (54% during 1981 to 1985 versus 44% during 1976 to 1980; P<0.001), the mean duration of delay (7.4 months) before the establishment of the diagnosis is still undesirably long. Greater public awareness is obviously needed. Awareness among the female population and the elderly are especially inadequate at present. More concerted efforts in educating the public on common presenting features and the importance of early presentation are vital. In addition, fellow colleagues should be more alert in considering this differential diagnosis to avoid undue delay. The presenting symptoms and signs which are outlined in Tables 1 and 2 should be duly recognised.

A thorough examination of the nasopharynx, and a serological test (serum IgA against the viral capsid

Table 4. Multivariate analysis of prognostic factors and disease-specific deaths using the Cox regression model

Prognostic factor	Disease-specific deaths		
	Hazard ratio	95% confidence interval	P value
Age (years)	1.012	1.009-1.016	<0.001
Sex (male, female)	0.880	0.838-0.924	<0.001
Treatment era (1981-85, 1976-80)	1.110	1.064-1.158	<0.001
Stage (I, II, III, IV, V)			<0.001
Radiotherapy (nil, incomplete, radical)			<0.001
Symptom duration (months)	1.003	0.999-1.008	0.142

antigen of the Epstein-Barr virus) should be offered to all patients with a persistent enlargement of the upper cervical lymph nodes, nasal symptoms, otological problems, headache or cranial nerve dysfunction. The latter two features are frequently mistaken as tension headache, temporal arteritis or diabetic neuropathy. A frustrating consequence of misdiagnosis is that patients with classic fifth and sixth nerve palsy are sometimes subjected to various fruitless investigations, such as computed tomography of the brain, which miss the detection of a nasopharyngeal lesion at the edges.

The association of otological symptoms with NPC is inadequately recognised. While only 20% of patients recorded this as the presenting complaint, 62% had tinnitus, serous otitis media and/or an impairment of hearing by the time of diagnosis. If patients have a more detailed otological assessment (including a pure tone audiogram), the incidence of abnormality would likely be even higher. More recent studies suggested that the incidence of otitis media could be as high as 40%.[15] It should also be noted that dermatomyositis is associated with prevalent malignancies,[16] and that this was the only symptom in 0.2% of the present series. The interval from detection of NPC could range from 1 to 1014 months (mean, 207 months). Hence, all patients with dermatomyositis should be thoroughly investigated and regularly followed up even if no apparent malignancy is found.

The importance of the early detection and diagnosis cannot be overemphasised. By improving the knowledge and awareness of this leading malignancy, any further delay in presentation will be minimised.

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