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Design of a prognostic index score for metastatic nasopharyngeal carcinoma☆

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Abstract

The survival outcome of patients with systemic cancer differs significantly between individuals even within the same tumour type. We set out to illustrate this by analysing the factors determining survival in patients with metastatic disease from nasopharyngeal carcinoma (NPC) and to design a scoring system based on these prognostic factors. Patients referred between January 1994 and December 1999 were retrospectively analysed. Factors analysed included patient (age group, gender, performance status (BS) at diagnosis of metastases), disease (number of metastatic sites, specific metastatic sites, disease-free interval (DFI), metastases at presentation, presence of locoregional recurrence), and laboratory factors (leucocyte count, haemoglobin level, albumin level). Univariate and multivariable analyses were performed using the Cox proportion hazards model. A numerical score was derived from the regression coefficients of each independent prognostic variable. The prognostic index score (PIS) of each patient was calculated by totalling up the scores of each independent variable. Independently significant, negative prognostic factors were liver metastasis, lung metastasis, anaemia, poor PS, distant metastasis at initial diagnosis, and a DFI of <6 months. Three prognostic groups based on the PIS were obtained: (i) good risk (PIS = 0–6); (ii) intermediate risk (7–10); (iii) poor risk ($\geqslant 11$). The median survivals for these groups were 19.5, 10, and 5.8, months, respectively, (log rank test: $P<0.0001$). The variable prognosis of patients with disseminated NPC can be assessed by using easily available clinical information (patient, disease and laboratory factors). The PIS system will need to be validated on prospectively collected data of another cohort of patients.

Keywords: Nasopharyngeal carcinoma; Metastasis; Prognosis; Prognostic index score

1. Introduction

The worldwide incidence of nasopharyngeal cancer (NPC) is low (<1 per 100 000), but it varies significantly among ethnic groups and geographical regions [1–5]. NPC is most prevalent in eastern Asia with the highest incidence reported among the Cantonese from the province of Guangdong, where rates range from 30 to 50 per 100 000 [5–7]. The incidence in Singapore is intermediate with the age-standardised incidence rate of 14.3 per 100 000 for males and 4.7 per 100 000 for females [8]. Most NPCs in endemic areas are of the World Health Organization (WHO) types II (non-keratinising carcinoma) and III (undifferentiated carcinoma) [5,9–13]. WHO type I (squamous cell carcinoma) is found in only 1–20% of all cases.

Endemic NPC is biologically different from squamous cell cancer of the head and neck. Systemic relapse, especially in those who present with locally advanced disease, is more commonly seen and tends to be more aggressive [10,14–17]. The bone is the most common site of distant failure, followed closely by the lungs and liver [11,12,18–21]. It is not uncommon to encounter patients with metastases to all of these three major sites. Thirty to sixty per cent of patients with NPC will develop distant metastasis and die of disseminated disease

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[10–12,14–17,21–29]. The predictors of distant metastasis and survival in treated NPC have been extensively studied and published [15–18,22–27,30–36]. However, there has been only one report that specifically examined the prognosticators of metastatic survival (survival subsequent to the diagnosis of distant metastasis) [12]. As with other solid tumours, NPC with distant metastases form a very heterogeneous group in which the duration of metastatic survival can vary considerably, ranging from 20 days to 26.8 months in our local experience [11]. Others have reported long-term disease-free survival in excess of 60 months in patients with solitary intrathoracic metastasis treated aggressively with multimodality therapy [12]. In one study of patients with metastatic NPC, Fandi and colleagues described 14 patients who had a long-term disease-free survival of 82–190 months [37].

Because of this heterogeneity, the identification of prognostic factors that will be able to predict survival outcome in metastatic NPC becomes important from both a therapeutic and research point of view. This information will probably be helpful in improving the design of clinical trials involving patients with metastatic NPC and hopefully will provide a more accurate interpretation of the results. Thus, this retrospective study was undertaken to identify these determinants of metastatic survival and develop a prognostic instrument for disseminated NPC.

Although systemic therapy is widely employed to treat metastatic disease in this chemosensitive cancer, there is no randomised data on the impact of chemotherapy on survival. In this retrospective study, attempts were made to examine the effect of chemotherapy on survival using statistical methods to minimise inherent biases.

2. Patients and methods

390 patients with disseminated NPC were referred to our department between January 1994 and December 1999. So far, we have been able to retrieve data for 246 patients. Twenty-six were excluded from the survival analysis because of missing survival data, leaving 220 evaluable patients.

All patients had a histological confirmation of NPC and underwent computerised tomography (CT) scanning of the postnasal space, chest-X-ray (CXR) and/or CT scan of the chest, ultrasound or CT scan of the abdomen and bone nuclear imaging to assess the extent of systemic disease. Patients were classified into the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM stages retrospectively using the recorded clinical and radiological data.

Disease-free interval (DFI) refers to the time from the onset of primary radiotherapy to the time of relapse in patients who achieved a complete response. Patients with metastasis at presentation were analysed as a separate category from patients who presented with localised disease, but developed metastases at a later date in the multivariable analysis. All sites of metastasis at the onset of systemic failure were recorded. Metastatic survival is defined as the survival subsequent to the development of distant relapse: time from the first diagnosis of metastasis to the time of death. Patient's performance status and biochemical assessments were all measured at the time of diagnosis of metastatic disease. Chemotherapy primarily refers to systemic treatment administered in the context of metastatic cancer.

The survival status was verified as of 30 June 2000 using the best available means. This included checking the clinic attendance records, direct telecommunication with the patient or family and ascertaining the dates of death from Singapore's National Death Registry.

Overall metastatic survival and group-specific metastatic survival were plotted against time using the Kaplan–Meier method and differences in survival curves were compared using the log-rank test.

Univariate and multivariable analyses were performed using the Cox proportion hazards model. The multivariable analyses were undertaken with both forward and backward stepwise procedures for identifying the independent prognostic variables. Adjustment was made for the effect of chemotherapy use in all analyses. Factors that were considered for inclusion included patient factors (age group, gender, performance status at diagnosis of metastatic disease), disease factors (number of metastatic sites, specific metastatic sites, metastasis at presentation, DFI, presence of locoregional recurrence) and laboratory factors (leucocyte count, haemoglobin level, albumin level). In order to construct a prognostic index score (PIS), factors were entered as categorical values as far as possible to keep the computations simple, although categorisation inevitably results in some loss of information. $P \leqslant 0.1$ was used as the cut-off value of statistical significance for variable selection in the multivariable modelling, in order not to miss potentially important prognostic factors. Statistical significance remains conventionally defined as $P \leqslant 0.05$ in the univariate modelling. The regression coefficient of each independent prognostic variable (the β in the Cox regression equation $HR = e^{\beta}$) is then modified into an integer numerical value to construct a PIS.

3. Results

3.1. Patient and disease characteristics

There was a male preponderance (81%). 41 patients (21%) presented with distant metastases at initial diagnosis. The mean age at first diagnosis of primary disease

was 45.9 years (ranging from 22 to 75 years) and at metastasis was 47.7 years (ranging from 23 to 77 years). 44 patients (25%) developed locoregional relapse prior to systemic failure. Slightly more than half the patients had more than 1 site of metastasis and the bone was the most frequently involved site (74%). The mean DFI was 23.3 months (range 3–106 months). Details are shown in Tables 1 and 2.

All patients were offered chemotherapy as palliation. Most patients (78%) received at least one line of systemic treatment for their metastatic disease and 48 patients declined chemotherapy. Of the latter group, only 4 patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 3. First-line chemotherapy most frequently consisted of a combination of 5-fluorouracil and cisplatin (63%). 26% of patients received newer agents such as paclitaxel and gemcitabine either alone or in combination. The latter group was treated on study protocols that were ongoing at that time. The mean number of cycles administered was 4 (ranging from 1 to 11) and the mean dose intensity received was 0.99 (ranging from 0.74 to 1.00). The objective response rate (complete and partial responses) was 60 and 10% of the patients experienced a stabilisation of their disease. The mean duration of response was 4 months (ranging from 0 to 57 months). 81 patients went on to receive salvage chemotherapy when their cancer progressed further. Of the 11 patients with a poor PS at diagnosis, 10 had an ECOG PS of 3 and 1 had an ECOG PS of 4.

Four declined chemotherapy and the remaining 7 had a cisplatin/5-fluorouracil combination (4 patients), gemcitabine/5-fluorouracil continuous infusion combination (1 patient) gemcitabine single-agent (1 patient), and cisplatin single-agent (1 patient). The mean number of cycles (range 1–4 cycles) received by these 7 patients was two and two patients had a partial response that lasted 4 and 5 months, respectively.

3.2. Survival

A hundred and seventy-six deaths have occurred with 44 still alive as of 30 June 2000. The overall median

Table 1
Patients' characteristics

Characteristic	*n* (%)
Gender	
Female	42 (19)
Male	178 (81)
Age (years)	
<44	98 (45)
44–65	108 (49)
>65	14 (6)
Performance (ECOG)	
0–1	187 (85)
2	22 (10)
3–4	11 (5)
Albumin (g/l)[a]	
<40	156 (81)
⩾40	37 (19)
Haemoglobin (g/dl)[a]	
<12	129 (63)
⩾12	75 (37)
White cell (per 10^6 cells/l^3)	
<4000	28 (14)
4000–11 000	135 (67)
>11 000	40 (20)
Leucoerythroblastosis[a]	
Present	18 (9)
Absent	184 (91)
Malignant fever[a]	
Present	15 (7)
Absent	204 (93)
Dermatomyositis[a]	
Present	4 (2)
Absent	215 (98)

ECOG, Eastern Cooperative Oncology Group.
[a] Some data are missing.

Table 2
Disease characteristics

Characteristic[a]	*n* (%)
Stage at 1st diagnosis	
I–II	49 (25)
III–IVB	108 (55)
IVC	41 (20)
Locoregional relapse	
Present	44 (25)
Absent	131 (75)
Disease-free interval (DFI)	
<6 months	158 (91)
⩾6 months	16 (9)
Bony metastasis	
Present	146 (74)
Absent	50 (26)
Liver metastasis	
Present	93 (43)
Absent	121 (57)
Lung metastasis	
Present	87 (40)
Absent	130 (60)
Skin metastasis	
Present	6 (3)
Absent	214 (97)
Distant nodal metastasis	
Present	69 (32)
Absent	144 (68)
No. of metastatic sites	
Single	99 (45)
Multiple	121 (55)

[a] Some data are missing in some of the subgroups.

metastatic survival was 11 months and the 2-year survival rate was 25% (Fig. 1). The median metastatic survival in the treated and untreated group was 13 and 8 months, respectively (Hazard Ratio [HR]: 0.48; $P=0.001$). This is shown in Fig. 2. When adjustments were made for both patient and disease variables this advantage remained significant (HR: 0.45; $P=0.01$).

3.3. Univariate analysis

Statistically significant, negative prognostic factors included female gender, hypoalbuminaemia, leucocytosis and liver metastasis. The results further show that anaemia (HR: 2.47), short DFI (HR: 2.48) and poor performance status (HR: 4.08) were associated with a particularly bad prognosis (Table 3).

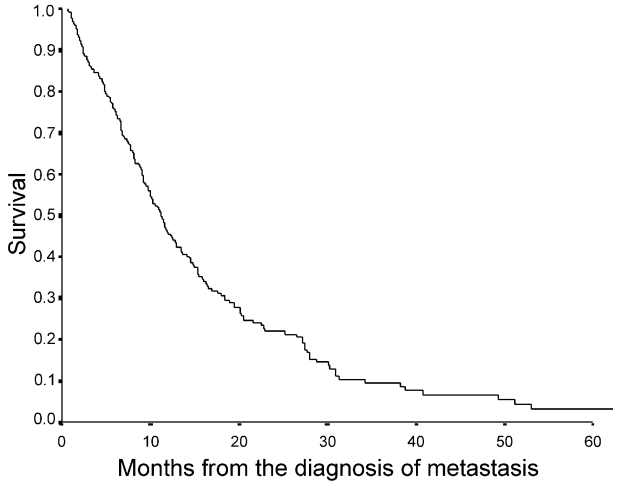

Fig. 1. Overall metastatic survival.

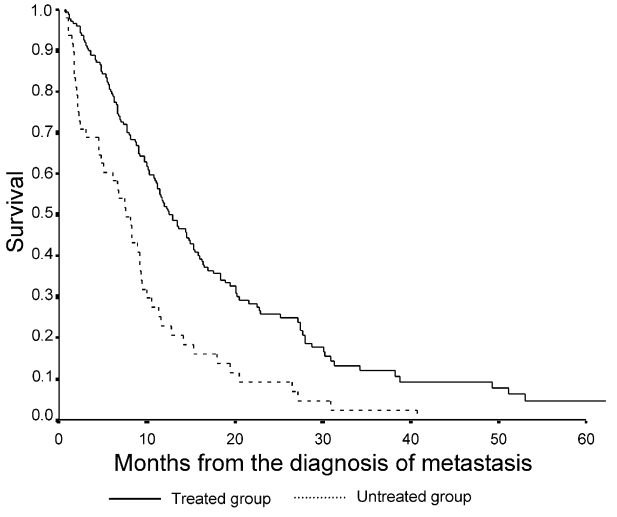

Fig. 2. Metastatic survival of the treated group vs. untreated group.

3.4. Multivariable analysis

Independently significant, negative prognostic factors were liver metastasis (HR: 1.4), lung metastasis (HR: 1.5), haemoglobin 120 g/l (HR: 2.1), PS $\geqslant$ECOG 2 (HR: 2.4), presence of metastasis at initial diagnosis (HR: 1.3) and a DFS of 6 months (HR: 2.4). These results and their 95% confidence intervals (CIs) are

Table 3
Univariate analysis of patient and disease variables

Factor	HR (95% CI)	*P* value
Gender		
Female	Baseline	
Male	0.64 (0.44–0.92)	0.022
Age (years)		
<44	Baseline	
44–65	1.22 (0.90–1.66)	
>65	1.57 (0.83–2.97)	
Performance		
PS 0–1	Baseline	
PS 2	2.36 (1.49–3.74)	
PS 3–4	4.08 (2.13–7.85)	Overall <0.0001
Albumin (g/l)		
<40	Baseline	
>40	1.65 (1.08–2.53)	0.015
Haemoglobin (g/dl)		
<12	Baseline	
$\geqslant$12	2.47 (1.75–3.50)	<0.0001
White cell (per 10^6 cells/l)		
<4000	Baseline	
4000–11 000	0.85 (0.54–1.33)	
>11 000	1.57 (0.93–2.64)	Overall 0.013
Leucoerythroblastosis	1.55 (0.92–2.60)	0.12
Fever	1.77 (1.02–3.06)	0.0595
Dermatomyositis	1.16 (0.37–3.64)	0.804
Stage at 1st diagnosis		
I–II	Baseline	
III–IVB	1.11 (0.77–1.62)	
IVC	1.36 (0.85–2.17)	Overall 0.44
Bony metastasis	1.28 (0.89–1.84)	0.174
Liver metastasis	1.54 (1.14–2.09)	0.0059
Lung metastasis	1.22 (0.89–1.65)	0.214
Skin metastasis	1.65 (0.67–4.04)	0.310
Distant nodal metastasis	0.74 (0.53–1.03)	0.069
No. of metastatic sites		
Single	Baseline	
Multiple	1.27 (0.94–1.71)	0.12
Locoregional relapse	1.06 (0.72–1.55)	0.56
Disease-free interval (DFI)		
>6 months	Baseline	
<6 months	2.48 (1.44–4.27)	0.01

95% CI, 95% Confidence Interval; HR, hazard ratio. PS, performance status.

Table 4
Significant independent variables from the multivariate analysis

Factor	HR (95% CI)	*P* value
Metastatic at onset	1.3 (0.84–2.1)	0.09
Liver metastasis	1.4 (0.96–2.1)	0.08
Lung metastasis	1.5 (1.0–2.2)	0.04
Anaemia (<120 g/l)	2.1 (1.4–3.2)	0.0002
ECOG ⩾2	2.4 (1.3–4.3)	0.005
DFI <6 months	2.4 (1.0–5.8)	0.09

shown in Table 4. Surprisingly, the presence of distant nodal metastasis conferred a favourable outcome with a relative hazard of 0.7 (95% CI 0.46–1.05; $P<0.001$).

3.5. Prognostic index score (PIS)

A numerical score is derived from the regression coefficients of each independent prognostic variable as described earlier. A score of 0 is assigned if the factor is absent or 1, 2 or 4 accordingly if present (see Table 5). Adjustment was made for the effect of chemotherapy use. The PIS for each individual patient is then calculated by totalling up the scores of each independent variable. The maximum score obtainable is 16. There were 200 patients with complete data for the computation of PIS. We were able to stratify them into 3 prognostic groups based on the PIS: (i) 75 patients in the good risk group (PIS = 0–6), (ii) 81 patients in the intermediate risk group (PIS = 7–10) and (iii) 44 patients in the poor risk group (PIS ⩾11). The median survivals for these groups were 19.5, 10 and 5.8 months, respectively, (log rank test: $P<0.0001$). The survival curves stratified by PIS groups are depicted in Fig. 3.

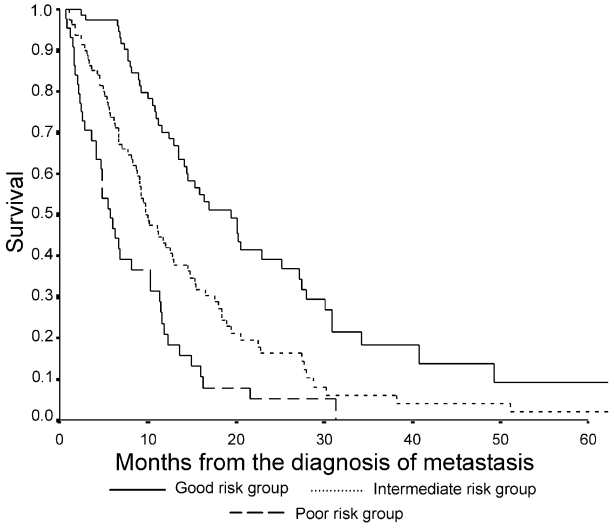

Fig. 3. Survival by prognostic index group.

Table 5
Prognostic index score

Factor	Score	β (HR = e^{β})
Metastasis at onset	1	0.28
Liver metastasis	2	0.35
Lung metastasis	2	0.41
Anaemia (<120 g/l)	4	0.76
ECOG ⩾2	4	0.87
DFI <6 months	4	0.89
Maximum score	16	

4. Discussion

This study demonstrates that survival following metastasis can be very variable and long-term survival is possible in some patients. In this study, survival following systemic relapse varied from <1 to 53 months. Two of the 44 patients who were still alive at the conclusion of this study have remained alive beyond 60 months.

Our findings concurred closely with those reported in the Hong Kong study [12]. We also observed that metastasis at presentation, short DFI and liver metastasis were factors associated with a poor prognosis and that survival was not significantly different with single compared with multiple sites of metastasis nor when preceded by locoregional recurrence compared with no such recurrence. However, the other study, our model has identified additional independent factors such as anaemia, lung metastases and a poor PS. The reason for this difference is the use of $P \leqslant 0.1$ as the cut-off for statistical significance in the multivariable analysis. Our results also revealed an unexpected finding: the presence of distant nodal metastasis was associated with a favourable prognosis. A closer dissection of the results failed to uncover any positive confounding associations with other prognostic variables that might have conferred this advantage. This discrepancy may be, in part, due to the less rigorous and non-uniform assessment of distant nodal disease and the inherent problems with the quality of retrospective data. For example, a CT scan of the chest was not routinely required in patients with radiographically-evident pulmonary secondaries on plain X-rays. Additionally, the different nodal sites may not have the same prognostic implications. Inguinal lymph node metastases may represent a more extensive spread than mediastinal nodal metastases. Due to this discrepancy, distant nodal disease was excluded from the construction of the current prognostic model. However, this issue will definitely need to be explored further in future prospective studies. As previously mentioned, the numerical score for each independent factor was derived by rounding-off the log of the HR to the nearest convenient integer. In deciding how much to round off, we had to compromise between oversimplification and loss of informational content. The present PIS is easy to

compute and distinctly stratifies the patients into different risk categories.

This study has illustrated two important points. Firstly, the prognosis of patients with metastatic NPC is probably reflected by the combined effects of various factors (categorised here as patient, disease and laboratory factors). How the disease will affect the patient can potentially be predicted by analysing these factors not singly, but in combination. Secondly, these factors are widely and easily available, and are routinely analysed or recorded in the course of managing these patients. Hence being able to use these routine factors to predict outcome is clearly advantageous.

No randomised studies have ever been done to compare chemotherapy with best supportive care in metastatic NPC. Using multivariable analysis, chemotherapy appeared to confer a significant survival advantage that is independent of the other possible confounding variables. However, we recognise that there could still be residual "confounding by indication" i.e. there may be differences affected by the therapeutic decision and that a randomised controlled trial remains the gold standard. Given the deeply entrenched, prevailing practice and the high chemoresponsiveness of NPC, it is doubtful that such a randomised study will ever be conducted.

We have embarked on a prospective study to verify the prognostic factors and to validate the PIS. Upon validation, this scoring system would help in a more accurate assessment of a patient's prognosis in the clinical setting. In the research setting, such a system would help in the stratification of patients and a more measured interpretation of the results of any therapeutic manoeuvres. It is conceivable that a similar scoring system could be designed for other solid tumors as well.

5. Conflict of interest statement

No financial and personal relationships with other people or organisations were involved in this study.

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