

Survival Prognostication in Patients with Skeletal Metastases from Nasopharyngeal Carcinoma: An Evaluation of the Scandinavian Sarcoma Group, Katagiri and Bauer Scoring Systems

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Abstract

Introduction: Nasopharyngeal carcinoma (NPC) is characterised by early metastases with the skeleton being the most common site of metastases. The ability to prognosticate survival is crucial in the decision whether or not to offer surgery to these patients and the choice of surgery offered. We aimed to evaluate the scoring systems namely: Bauer, Katagiri and Scandinavian Sarcoma Group (SSG) in NPC patients with skeletal metastases. **Materials and Methods:** A total of 92 patients with skeletal metastases from NPC were studied. We retrospectively analysed the actual survival of these patients and compared with predicted survival according to the 3 scoring systems. The predicted survival according to each system was calculated and labelled as A scores. These were then re-scored by assigning NPC as a better prognostic tumour and labelled as B scores. The predicted survival of scores A and B were compared to actual survival. Univariate and multivariate Cox regression analyses were performed. The predictive values of each scoring system were calculated. **Results:** The median overall survival for the whole cohort was 13 months (range: 1 to 120 months). In multivariate analysis, general condition and visceral metastases showed significant effect on survival. There were statistically significant differences ($P < 0.001$) between the subgroups of the SSG B as well as Katagiri B scoring systems where NPC was classified as a better prognostic tumour. SSG B provided the highest predictive value (0.67) as compared to the other 2 scoring systems. **Conclusion:** The SSG and Katagiri score could be used to prognosticate NPC with a statistically significant association with actual survival.

Ann Acad Med Singapore 2016;45:51-60

Key words: Bone metastases, Nasopharyngeal cancer, Survival Prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a cancer characterised by marked geographical differences in distribution; it is endemic in Southern China and Southeast Asia. Chinese people living in areas of Southern China (including Hong Kong) have a higher incidence of NPC compared with Chinese migrants living overseas.¹ In Hong Kong, NPC is the fourth most common malignancy and in Singapore, it is the eighth most common cancer among males.² Despite the low incidence of NPC in Europe and the United States (US),^{3,4} when high risk or intermediate risk persons migrate to lower risk countries, their incidence of NPC remains much higher than those of other races.¹ Among Chinese immigrants to the US, the incidence of

NPC is as high as 9.9 per 100,000 population which is comparable to 12.8 per 100,000 population in Singapore.⁵

NPC is reported to have a high incidence of early metastases, with metastases being present in 11% of patients at diagnosis. The skeleton is the most common site of metastases in 70% to 80% of NPC patients.⁶ Skeletal metastases can present with intractable pain, pathological fractures and/or paralysis in the spinal metastases.⁷ The survival of patients with skeletal metastases has improved due to better oncological treatments; predisposing patients to increased risk of skeletal-related complications. Surgery is an important modality of treatment for addressing skeletal-related complications. The decision regarding choice of treatment especially surgery in patients with skeletal

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metastases is influenced by estimated patient survival.^{8,9}

There have been several prognostic systems developed for the prognostication of patients with skeletal metastases; these include the scoring systems of Bauer,¹⁰ Katagiri¹¹ and the Scandinavian Sarcoma Group (SSG).¹² The Bauer score and its modification have been validated in the prognostication of metastatic disease to the spine,¹³ while the Katagiri score has also been validated in patients with bone metastases to the proximal femur.¹⁴ The SSG score was developed based on a retrospective study of 1195 surgically treated patients with skeletal metastases and an analysis of prognostic factors suggested by other prognostic scores.¹² It is suggested to be a reliable and simple prognostic tool; however its use has not been validated before. We note that none of these scoring systems have been validated in NPC and that NPC is not included as a site of primary tumour in all of these systems. We hereby aim to determine reliability of the above scoring systems in predicting survival by categorising NPC as both a better or worse prognostic factor. We also aim to investigate the prognostic factors for survival in NPC patients with skeletal metastases based on the findings in our cohort.

Materials and Methods

Patients and Data Collection

We retrospectively analysed all patients, with histologically proven NPC, who were treated in our institution. A total of 814 patients with NPC were identified between January 2007 to December 2011 by searching the hospital electronic records. A total of 92 patients were diagnosed with skeletal metastases. Retrospective data collection began on 1 July 2013 which ensured all patients had been followed up till death or at least 1 year. This study was approved by an institutional ethics review board. Diagnosis of skeletal metastases was made radiologically by one or more of the following modalities: magnetic resonance imaging (MRI), computed tomography (CT) and bone scan. In operated cases, bone biopsies for histological diagnosis were also taken. Patient data were collected for the demographic characteristics, tumour histology, general and specific clinical findings in relationship to the primary tumour and skeletal metastases. These specific findings included the general condition in terms of Karnofsky's performance score (KPS) and Eastern Cooperative Oncology Group (ECOG) score, number of skeletal metastases, number of visceral metastases, presence or absence of pathological fractures, as well as type of treatment received, i.e. either chemotherapy received or not. Some or all of these factors mentioned above are included in the various scoring systems, which we planned to study. Data required for scoring patient prognosis was available for all the patients on review of electronic records or case notes and no telephone interview/

call backs were needed. On the basis of these findings, we retrospectively calculated the Bauer,¹⁰ Katagiri¹¹ and SSG survival score¹² of these patients. The scores were calculated by the first and second authors of the paper independently with the patients' identity and actual survival blinded. Neither of these authors has been directly involved in patient care. If the scores calculated for a patient were different, the patient was re-evaluated by the 2 authors and the consensus score was used. We also analysed the influence of age, sex, race, and the above mentioned specific findings on survival. The survival period was calculated from the date of diagnosis of the skeletal metastases until death or end of the study period.

Survival Score Calculation

Scandinavian Sarcoma Group (SSG) Score

The SSG score (Supplementary Table 1) is based on 4 prognostic factors: number of skeletal metastases, presence of organ metastases, Karnofsky score and type of primary tumour. A better prognostic score is given to the following primary tumours: breast, kidney, thyroid, lymphoma and myeloma. Therefore, NPC scored worse in this category and the overall score obtained was labelled as SSG A. We then re-scored the patients by assigning NPC as a positive prognostic factor and labelled the score obtained as SSG B. The SSG divides patients into 3 scoring subgroups, with a score of 4-3, 2-1 and 0 respectively and an estimated survival of more than 6 months, 3 to 6 months and less than 3 months respectively.

Katagiri Score

In the Katagiri scoring system (Supplementary Table 2), patients are scored according to the following prognostic factors: primary tumour, presence of visceral/cerebral metastases, ECOG performance status, previous chemotherapy and presence of multiple skeletal metastases. Primary tumours are divided based on speed of growth into slow growth, moderate growth and fast growth tumours. NPC is not directly included in this scoring system, therefore, we included it in the category of primary tumour labelled as "moderate growth (other carcinoma/sarcoma)". The overall score was labelled as Katagiri A. We then re-scored the patients by assigning NPC as a slow growth tumour (better prognostic tumour) and labelled this score Katagiri B. In the Katagiri score, patients are divided into 3 scoring subgroups: 0-2, 3-5, and 6-8. The survival rate for patients in each subgroup is 0.98, 0.71, and 0.31 respectively at 6 months, and 0.89, 0.49, and 0.11, respectively at 12 months.

Bauer Score

In the Bauer score (Supplementary Table 3), patients are

scored according to the following 5 positive prognostic factors: absence of visceral metastases, and absence of pathological fracture, solitary skeletal metastases, not primary lung cancer and the presence of the following primary tumours, breast, kidney, lymphoma and myeloma. Therefore, NPC scores lower as it does not fall in Bauer scoring system. We scored the patient's based on the original Bauer score and labelled this score Bauer A. After which, we proceeded to re-score the patients by including NPC in the primary tumour group, giving it a better prognostic score and labelling this score as Bauer B. Patients can be categorised into 3 scoring subgroups: patients with a score of 4-5 having a 1-year survival rate of 0.5, patients with a score of 2-3 having a 1-year survival rate of 0.25 and patients with a score of 0-1 died within 6 months of surgery.

Statistical Analysis

Survival analysis was performed with Stata Statistical software version 12. Univariate and multivariate Cox regression analyses were performed to evaluate the prognostic values of each demographic and clinical parameter on survival. Cox regression analyses, Kaplan-Meier survival estimates and log rank tests were completed for all scoring systems (A and B). Predictive values of each scoring system were measured by building receiver operating characteristics (ROC) curves using postestimation commands after Cox regression analyses. Comparison of AUCs for each scoring systems (A and B) were made using "c" statistics. Likelihood ratio test Bayesian information criterion (BIC) was also applied to compare the scoring systems in predicting survival. *P* value of less than 0.05 was considered to be statistically significant for all analyses.

Results

Our study population included a total of 92 patients in the final analysis. Table 1 demonstrates the details of patients' demographic characteristics, and clinical parameters that have potential impact on survival. Of note is the preponderance of male and Chinese patients as well as the good general condition of the patients in terms of Karnofsky score and ECOG score. In this cohort of patients, 82 patients had multiple skeletal metastases at diagnosis.

In our study, 87 (95%) patients had spinal metastases, 71 (77%) had axial metastases (skull and pelvis) and 36 (39%) had appendicular metastases. Of these patients, 8/87 of the patients with spinal metastases required surgical treatment for either cord compression or instability and 28/87 of these patients required palliative radiotherapy for pain due to spinal metastases. Only 2 of the patients with axial metastases required acetabular reconstruction for acetabular metastases and only 1 patient required open reduction

Table 1. Demographic Characteristics and Clinical Features of the Study Patients

		Frequency	Percentage
Age	Median – 52 (range: 26-90)		
Gender	Male	73	79
	Female	19	21
Race	Chinese	77	84
	Non-Chinese (Malay & others)	15	16
General condition (KPS)	<70	28	30
	≥70	64	70
General condition (ECOG)	3-4	28	30
	0-2	64	70
No. of skeletal metastases	Single	10	11
	Multiple	82	89
Visceral metastases	Absent	32	35
	Present	60	65
Pathological fracture	No	67	73
	Yes	25	27
Chemotherapy	No	60	65
	Yes	32	35

KPS: Karnofsky performance scale; ECOG: Eastern Cooperative Oncology Group

internal fixation of the femur with an intramedullary device for a pathological femur fracture.

Table 2 demonstrates the number of patients alive or dead for subgroup in each of the 3 scoring systems. As for evaluation of independent significant prognostic factors, the univariate analysis revealed that general condition (either KPS or ECOG) and the presence of visceral metastasis have a statistically significant effect on survival. There was collinearity between KPS and ECOG, and hence KPS was omitted in the multivariate model. In multivariate analysis, adjusting for variables, which were significant in univariate analysis, all the same parameters were found to be significant, independent prognostic factors. The highest hazard ratio (6.37, 95% CI, 3.32 to 12.18) was found in ECOG performance status scale category of 3-4. This shows that the patients with ECOG score of 3 or 4 were 6.37 times more likely to die in a year from diagnosis than those with more favourable score of 0-2. Regarding visceral metastases, the hazard ratio was 3.04 in the group with visceral metastases. This reveals that patients who had visceral metastases were 3.04 times more likely to die in a year from diagnosis than those without visceral metastases. The prognostic values of specific parameters according to the univariate and multivariate Cox regression analyses are presented in Table 3.

Table 2. Patients' Survival in Each Scoring System Subgroup at the End of the Study

Scoring System	No. of Patients Alive (%)	No. of Patients Dead (%)	Scoring System	No. of Patients Alive (%)	No. of Patients Dead (%)
SSG A			SSG B		
Score 3-4	1 (33%)	2 (67%)	Score 3-4	20 (63%)	12 (37%)
Score 1-2	33 (49%)	35 (51%)	Score 1-2	17 (29%)	41 (71%)
Score 0	3 (16%)	16 (84%)	Score 0	-	-
Katagiri A			Katagiri B		
Score 0-2	1 (20%)	4 (80%)	Score 0-2	21 (55%)	17 (45%)
Score 3-5	26 (50%)	26 (50%)	Score 3-5	16 (31%)	36 (69%)
Score 6-8	10 (30%)	23 (70%)	Score 6-8	-	-
Bauer A			Bauer B		
Score 4-5	5 (71%)	2 (29%)	Score 4-5	15 (48%)	16 (52%)
Score 2-3	29 (40%)	43 (60%)	Score 2-3	22 (37%)	37 (63%)
Score 0-1	3 (27%)	8 (73%)	Score 0-1	-	-

SSG: Scandinavian Sarcoma Group

Actual Survival Time and Total Scores

The median overall survival time was 13 months (range: 1 to 120 months) from diagnosis of skeletal metastases. At the time of analysis, 15 (16%) patients had survived less than 3 months, 12 (13%) patients had survived 36 months and 65 (71%) patients had survived more than 6 months. The actual and predicted survivals of 3 scoring systems are presented in Table 4.

I. Scandinavian Sarcoma Group (SSG) Score

In this scoring system (Supplementary Table 1), a higher score provides a more favourable prognosis. The median SSG A score was 1 (range: 0-4) while the median SSG score B was 2 (range: 1-4). In SSG A score, 21 (23%) patients had a score of 0, while 68 (74%) patients had a score of 1-2 and 3 (3%) patients had a score of 3-4. In SSG B score, 61

Table 3. Univariate and Multivariate Analyses of Prognostic Value of Demographic and Clinical Parameters

Prognostic Factors	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
General condition (KPS)						
<70 (reference [†])	1	-	-			
≥70	0.15	0.08 – 0.29	<0.001*			
General condition (ECOG)						
0 – 2 (reference [†])	1	-	-	1	-	-
3 – 4	6.31	3.36 – 11.83	<0.001*	6.37	3.32 – 12.18	<0.001*
No. of skeletal metastases						
Single (reference [†])	1	-	-			
Multiple	0.84	0.36 – 1.98	0.69			
Visceral Metastases						
Absent (reference [†])	1	-	-	1	-	-
Present	3.09	1.58 – 6.02	0.001*	3.04	1.54 – 5.98	0.001*
Pathological fracture	0.89	0.49 – 1.62	0.7			
Chemotherapy	1.66	0.93 – 2.97	0.08			
Age	0.99	0.97 – 1.02	0.96			
Sex	1.17	0.55 – 2.50	0.67			
Race	1.11	0.61 – 2.03	0.72			

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance scale

*Significant P value <0.05.

[†]Refers to baseline to which the other respective categories are compared.

Table 4. Actual and Predicted Survival of the Patients

Scoring System	Predicted Survival*	Actual Survival*
SSG A		
>6 months	52 (56.5%)	68 (73.9%)
>12 months	32 (34.8%)	49 (53.3%)
SSG B		
>6 months	75 (81.5%)	68 (73.9%)
>12 months	50 (54.4%)	49 (53.3%)
Katagiri A		
>6 months	3 (3.3%)	68 (73.9%)
Katagiri B		
>6 months	31 (33.7%)	68 (73.9%)
Bauer A		
>12 months	21 (22.8%)	49 (53.3%)
Bauer B		
>12 months	31 (33.7%)	49 (53.3%)

SSG: Scandinavian Sarcoma Group

*Values are given as the number of patients with the percentage in parentheses.

(66%) patients had a score of 1-2 and 31 (34%) patients had a score of 3-4; there were no patients who had a score of 0 (predicted survival of less than 3 months). The estimated survival for the majority of patients using both SSG A score and SSG B score was 3 to 6 months.

II. Katagiri Score

In this scoring system (Supplementary Table 2), a lower score provides a more favourable prognosis. The median Katagiri A score was 5 (range: 0-8), 2 (2%) patients had a score of 0-2, 54 (59%) patients had a score of 3-5 and 36

(39%) patients had a score of 6-8. The median Katagiri B score was 3 (range: 0-5), 37 (40%) patients had a score of 0-2 while 55 (60%) had a score of 3-5; none of the patients had a score of 6-8. The predicted survival rate for the majority of the patients using both Katagiri A score and Katagiri B score was 0.71 at 6 months and 0.49 at 12 months.

III. Bauer Score

In this scoring system (Supplementary Table 3), a higher score provides a more favourable prognosis. The median Bauer A score was 2 (range: 0-5) while the median Bauer B score was 3 (range: 2-5). In the Bauer A score, 12 (13%) patients had a score of 0-1 points, while 75 (82%) patients had a score of 2-3 points and 5 (5%) patients had a score of 4-5 points. In the Bauer B, none of the patients had a score of 0-1 points, while 62 (67%) patients had a score of 2-3 points and 30 (33%) patients had a score of 4-5 points. Using both Bauer A score and Bauer B score, the majority of patients had one 1-year survival rate of 0.25.

Evaluation of the Scoring Systems

Cox regression analyses showed that the absolute score of SSG and Katagiri scoring systems (either A or B) was significantly associated with the actual survival in all 92 patients. The higher score in SSG scoring system was associated with longer survival. The higher score in Katagiri scoring system was associated with poor survival. Each scoring system classifies the patients into different prognostic subgroups depending on the scores. We calculated the hazard ratios for each scoring subgroup within each scoring system and demonstrated the results in Table 5. The best prognostic score was used as a reference

Table 5. Cox Regression Analysis of Three Scoring Systems

Scoring System	Hazard Ratio	95 % CI	P Value	Scoring System	Hazard Ratio	95 % CI	P Value
SSG A	0.29	0.19 – 0.47	<0.001*	SSG B	0.29	0.19 – 0.47	<0.001*
Score 3-4 (reference†)	1	-	-	Score 3-4 (reference)	1	-	-
Score 1-2	0.31	0.07 – 1.32	0.11	Score 1-2	4.03	2.02 – 8.03	<0.001*
Score 0	2.24	0.51 – 9.82	0.29	Score 0	No patients		
Katagiri A	1.51	1.19 – 1.92	0.001*	Katagiri B	1.58	1.25 – 2.01	<0.001*
Score 0-2 (reference†)	1	-	-	Score 0-2 (reference)	1	-	-
Score 3-5	0.19	0.06 – 0.58	0.003*	Score 3-5	2.56	1.39 – 4.69	0.002*
Score 6-8	0.65	0.22 – 1.89	0.43	Score 6-8	No patients		
Bauer A	0.78	0.56 – 1.08	0.13	Bauer B	0.78	0.56 – 1.08	0.1
Score 4-5 (reference†)	1	-	-	Score 4-5 (reference)	1	-	-
Score 2-3	2.97	0.72 – 12.36	0.13	Score 2-3	1.67	0.91 – 3.05	0.09
Score 0-1	2.74	0.58 – 12.96	0.20	Score 0-1	No patients		

*Significant P value <0.05.

†Refers to baseline to which the other respective score subgroups are compared.

value of 1. The best prognostic scoring subgroup was 3-4 in SSG, 0-2 in Katagiri and 4-5 in Bauer. Statistical analysis revealed that 1 subgroup of Katagiri A (subgroup score 3-5), all subgroups of SSG B as well as Katagiri B scoring systems were significantly associated with the actual survival. However, there were no significant association between the subgroups of SSG A, Bauer A as well as B and actual survival. Bauer A (score 2-3 and score 0-1) tended to predict worse survival compared to score 4-5, however, the considerable effect size did not reach statistically significant level.

Kaplan Meier curves and log rank tests of all the scoring systems (A and B) are demonstrated in Figures 1a-f. Log rank test revealed that there were statistically significant differences in survival between the different prognostic subgroups of SSG and Katagiri scoring systems ($P < 0.001$). Bauer scoring system showed no correlation between predicted and actual survival.

Predictive Values of the Scoring Systems

Predictive abilities of the scoring systems (A and B) measured by ROC, are presented as area under curve (AUC) in Table 6. The predictive value of SSG B, Katagiri B and Bauer B were higher as compared to that of respective SSG A, Katagiri A and Bauer A. However, no statistically significant difference was observed between the 2 AUCs of the scoring systems A and B for all 3 scoring systems. Among all these scoring systems, SSG B provided the highest predictive value (0.67) as compared to the other 2 scoring systems. Where likelihood ratio test was concerned, the smallest BIC was observed in SSG scoring systems A and B.

Discussion

NPC is a cancer that is sensitive to both radiotherapy and chemotherapy. In patients with metastatic disease, chemotherapy can achieve 50% to 80% response rates with a median time to progression of disease of 5 to 11 months and median survival of 12 to 20 months which is similar to the median survival of our cohort of 13 months.^{3,4}

The ability to prognosticate survival is crucial in the decision whether or not to offer surgery to a patient and the choice of surgery offered. Numerous prognostic scoring systems have been proposed to prognosticate the survival of patients with skeletal and spinal metastases, but as yet, none have been validated in NPC.^{9-12,15-17}

There are a wide variety of surgical options available for the treatment of skeletal metastases and the goals of surgery include pain relief, restoration of function, mobility and improvement of quality of life. Pathological fractures are prone to non-union or delayed union due to increased

Table 6. Predictive Values of Scoring Systems

Scoring System	AUC	SE	Likelihood Ratio Test BIC	P Value*
SSG A	0.59	0.04	391.7	0.21
SSG B	0.67	0.04	391.7	
Katagiri A	0.61	0.05	404.7	0.81
Katagiri B	0.62	0.05	400.8	
Bauer A	0.52	0.04	405.9	0.64
Bauer B	0.55	0.05	405.9	

AUC: Area under curve; BIC: Bayesian information criterion; SE: Standard error; SSG: Scandinavian Sarcoma Group

*P value from 'c' statistics showing difference between 2 AUCs in ROC.

osteoclast activation by tumour cell factors produced by the primary tumour. The choice of surgery must take the palliative nature of the surgery into account and not subject a patient with a short life expectancy to a radical procedure for which recovery and rehabilitation time is longer than the patient's life expectancy; at the same time, in view of the expected poor healing, implant failure and repeated surgery must be avoided by choosing the appropriate implant and surgery in a patient with a longer life expectancy.^{8,18} Patients with a life expectancy of less than 6 weeks are unlikely to benefit from elective surgery while those with a prognosis of more than 6 weeks should be considered for internal fixation and stabilisation, patients predicted to survive more than 6 months may even be considered for metastatic resection and reconstruction. Thus, it is important to find an appropriate prognostic scoring system to accurately predict patient survival to determine the appropriate choice of surgery for each patient with metastatic bone disease.

The Bauer score is the only system of the 3 studied systems, which makes use of the presence of pathological fractures as a prognostic factor. Although the presence of pathological fractures has been found to be a significant survival prognostic factor in some studies,^{7,19} it was not found to be a significant prognostic factor in our study group on univariate and multivariate analysis. This could be the reason why the Bauer score was not found to be associated with actual survival in our study. It is of note that in a multivariate analysis of 7 spinal metastases survival scoring systems by Leithner et al,¹³ a modified Bauer score without the inclusion of pathological fractures as a prognostic factor was found to be the most highly predictive of survival in spinal metastases.

The Katagiri score¹¹ is similar to the Bauer score¹⁰ and the SSG score¹² in that it makes use of primary tumour type, presence of visceral/cerebral metastases and multiple skeletal metastases as prognostic factors. However, it makes use of the ECOG score as a measure of functional status

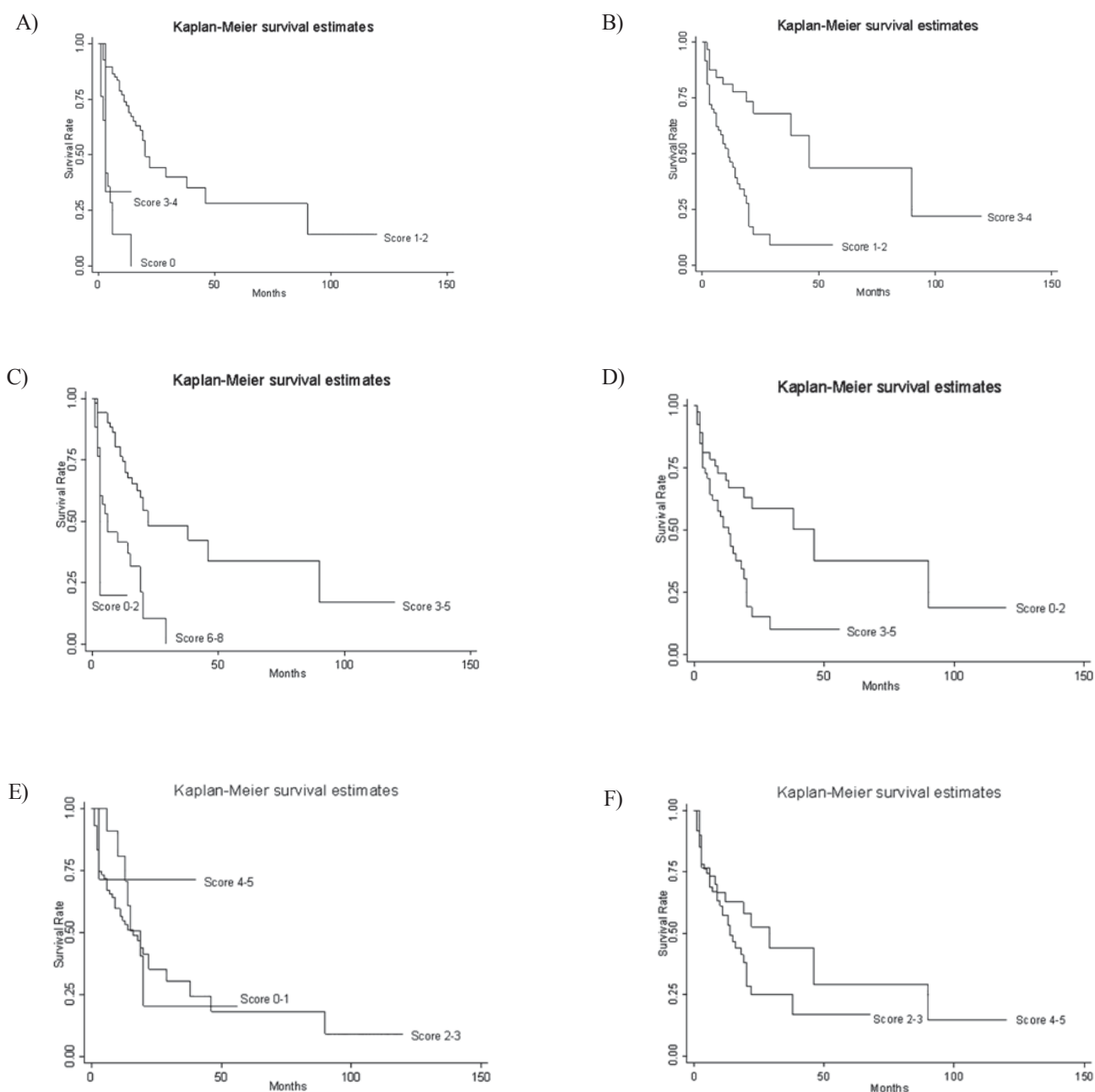


Fig. 1. Kaplan-Meier survival curves. A) for SSG A; B) for SSG B; C) for Katagiri A; D) for Katagiri B; E) for Bauer A; and F) for Bauer B.

and previous chemotherapy is considered a poor prognostic factor. A history of previous chemotherapy may indicate an advanced NPC as chemotherapy is usually prescribed only in advanced disease, and secondly patients who have already received chemotherapy prior to treatment may have fewer treatment options once skeletal metastases are diagnosed.¹¹ Chemotherapy was not found to be a significant prognostic factor for survival in our cohort. The ECOG score however

was found to be a significant prognostic factor for survival in both univariate and multivariate analyses.

In our study, performance status (both Karnofsky and ECOG scores) and visceral metastases were found to be significant predictive factors of survival. These factors were part of each of the 3 scoring systems analysed. These findings correlate with a study by Nathan et al⁹ which showed that after clinician assessment and haemoglobin

levels, number of visceral metastases, performance score, primary diagnosis and number of skeletal metastases are the most accurate predictors of survival. Of note is the finding that multiple skeletal metastases is not a predictive factor for survival in our cohort. We feel that it can be explained by the fact that 82 (89.13%) patients in our cohort had multiple bony metastases at presentation, making it a poor prognostication tool.

Through our search of PubMed index articles on NPC with skeletal metastases, we could not find any previous studies that evaluate the predictive value of the various prognostic scoring systems in this group of patients. The absolute score of SSG and the Katagiri scoring system both had statistically significant ($P < 0.001$) association with survival on Cox regression analysis and there was statistically significant difference in survival between each subgroup of the SSG B as well as Katagiri B scoring systems where NPC was classified as a good prognostic tumour. Although the difference between the AUCs of SSG A and B, as well as Katagiri A and B, were not statistically significant, the predictive value of SSG B and Katagiri B are higher than that of SSG A and Katagiri A respectively with the highest predictive probability observed in SSG B (AUC: 0.67). By looking at the likelihood ratio test BIC, the smallest BIC (i.e. prediction is the closest to true model) was observed in SSG scoring system A and B. By also analysing the predicted and actual survival in Table 4, it was noticeable that the predicted 1-year survival by SSG B was the closest to the actual 1-year survival. Hence, the SSG B score appears to be better in predicting survival compared to Katagiri and Bauer scores.

In our study, NPC patients tended to have good general condition (69% of patients had KPS score of ≥ 70 and ECOG score of 0-2) despite the majority of these patients presenting with multiple skeletal metastases as well as visceral metastases. Moreover, in NPC patients, the median survival time is 13 months and 70.66% of our patients survived more than 6 months. All of the above suggests that when prognosticating NPC, it would be more appropriate to treat “NPC as a tumour with a relatively good prognosis”.

Our study highlights that both the Katagiri and SSG scoring systems can be used; the SSG scoring system with our suggested modification (NPC as a tumour with better prognosis) appears to be the most accurate of these 3 systems in prognosticating the patients with metastatic skeletal disease from NPC. This is the first study to validate the above scoring systems for the prognostication of NPC patients with skeletal metastases. We recommend that one must interpret these scores with caution as the AUC is less than 0.80, which is the minimum AUC needed to consider a test to be a good one. At present, we suggest that clinical decision-making should rely on individual patient factors

such as the patients’ general condition and tumour load represented by presence of visceral metastases.

Strength and Limitation

Our retrospective study design is a limitation, however, given that we analysed patients with skeletal metastases from a single primary cancer namely NPC, we could minimise population heterogeneity in our study.

Conclusion

In conclusion, our study shows that NPC patients with skeletal metastases have median survival of 13 months from the diagnosis of skeletal metastases. It was observed that visceral metastases and general condition (either Karnofsky performance status or ECOG) have significant impact on survival. Katagiri and SSG scoring systems could be used to prognosticate the survival of these patients, with the SSG B scoring system appearing to be the most accurate predictor of survival. Larger studies, which assess NPC as a positive prognostic factor in SSG scoring system should be done to validate this prognostic system for metastatic NPC.

Acknowledgement

The authors would like to thank Dr Deepti Nayak, Novia Tan and Georgina Kwek, for their massive contribution in data collection of the nasopharyngeal carcinoma patients; and A/Prof Thomas Loh for his guidance while doing the study.

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Supplementary Table 1. Scandinavian Sarcoma Group (SSG) Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
Number of skeletal metastases		Number of skeletal metastases	
Single	1	Single	1
Multiple	0	Multiple	0
Presence of organ metastases		Presence of organ metastases	
Absent	1	Absent	1
Present	0	Present	0
Breast cancer, kidney cancer, thyroid cancer, myeloma, lymphoma		Breast cancer, kidney cancer, thyroid cancer, myeloma, lymphoma, NPC	
Yes	1	Yes	1
No	0	No	0
Karnofsky score		Karnofsky score	
≥70	1	≥70	1
<70	0	<70	0
Estimated survival: 0 point – less than 3 months; 1-2 points – 3-6 months; 3-4 points – more than 6-12 months			

NPC: Nasopharyngeal carcinoma

*NPC was not stated in this score.

†NPC, assigned as a positive prognostic factor with a score of 1 (in view of the known good prognosis for NPC).

Supplementary Table 2. Katagiri Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
Primary lesion		Primary lesion	
Rapid growth (hepatocellular, gastric, lung carcinoma)	3	Rapid growth (hepatocellular, gastric, lung carcinoma)	3
Moderate growth (other carcinoma and sarcoma, NPC)	2	Moderate growth (other carcinoma and sarcoma)	2
Slow growth (breast, prostate, thyroid carcinoma, multiple myeloma, malignant lymphoma)	0	Slow growth (breast, prostate, thyroid carcinoma, multiple myeloma, malignant lymphoma, NPC)	0
Visceral or cerebral metastases	2	Visceral or cerebral metastases	2
Performance status (ECOG) 3 or 4	1	Performance status (ECOG)* 3 or 4	1
Previous chemotherapy	1	Previous chemotherapy	1
Multiple skeletal metastases	1	Multiple skeletal metastases	1
Estimated survival rate at 6 months: 0-2 points – 0.98; 3-5 points – 0.71; 6-8 points – 0.31 12 months: 0-2 points – 0.89; 3-5 points – 0.49; 6-8 points – 0.11 24 months: 0-2 points – 0.75; 3-5 points – 0.28; 6-8 points – 0.02			

ECOG: Eastern Cooperative Oncology Group; NPC: Nasopharyngeal carcinoma

*NPC, assigned under the moderate growth tumours with score of 2.

†NPC, assigned under the slow growth tumour with score of 0 (in view of the known good prognosis for NPC).

Supplementary Table 3. Bauer Scoring Systems A and B

Prognostic Factors	Score A*	Prognostic Factors	Score B†
No visceral metastases	1	No visceral metastases	1
No pathological fracture	1	No pathological fracture	1
Solitary skeletal metastases	1	Solitary skeletal metastases	1
Not primary lung cancer	1	Not primary lung cancer	1
Primary tumour (breast, kidney, lymphoma, multiple myeloma)	1	Primary tumour (breast, kidney, lymphoma, multiple myeloma, NPC)	1
Estimated one year survival rate: 0-1 point – died within 6 months of surgery; 2-3 points – 0.25; 4-5 points – 0.5			

NPC: Nasopharyngeal carcinoma

*NPC was not stated in this score.

†NPC, assigned as a positive prognostic factor with a score of 1 (in view of the known good prognosis for NPC).