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ORIGINAL RESEARCH

Surgical Treatment Outcomes of Spinal Metastases of Nasopharyngeal Carcinoma: The First Report of 30 Patients from a Single Center

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Background: Studies focused on surgical interventions of spinal metastases of nasopharyngeal carcinoma (SMNPC) are blank.

Methods: Patients with SMNPC who received surgical treatment in our center between 2005 and 2017 were included. Univariate and multivariate analysis of various clinical characteristics and operation-related data were analyzed to identify the independent factors that affected prognosis. Factors with P values of 0.1 or less were subjected to multivariate Cox regression analysis. P values of 0.05 or less were considered statistically significant.

Results: A total of 30 patients with SMNPC treated with surgery were included. The thoracic spine was the most frequently involved site. The patients in this series achieved good overall survival (OS, 20.26 months) with limited perioperative complications. The univariate analysis suggested that preoperative Karnofsky performance scale, number of spinal metastases, number of visceral metastases, preoperative Frankel score, surgical resection mode and Ki 67 were potential prognostic factors. In the multivariate analyses, number of visceral metastases, preoperative Frankel score and resection mode were found to be independent prognostic factors.

Conclusion: This is the first study focusing on surgical outcomes in SMNPC. The thoracic spine was the most frequently involved site of SMNPC. Preoperative Frankel score, number of visceral metastasis and surgical resection mode were independent prognostic factors for SMNPC. Combined with adjuvant therapies, surgical interventions should be recommended early when necessary.

Keywords: nasopharyngeal carcinoma, metastasis, spine, prognostic factor, surgical treatment

Introduction

Nasopharyngeal carcinoma (NPC) is an uncommon tumor throughout the world, and it is the most commonly diagnosed head and neck malignancy in southern China, with an incidence of 25 per 10,000.[1–3] The widely accepted classification by the WHO divides NPC into 3 categories, I, II and III.[4] More than 95% have tumors that fall into WHO type III (undifferentiated), and these are more radiosensitive and have a better prognosis than tumors in other WHO groups. WHO type I and WHO type II tumors are associated with alcohol and tobacco use, are commonly found in nonendemic regions and have a poorer prognosis.[4] With the application of intensity-modulated radiotherapy (IMRT), the locoregional control of NPC has improved dramatically with an overall survival (OS) of 80–90.5% at 5 years.[5,6] Nevertheless, distant metastasis (DM) remains the main reason for therapeutic failure.[7–9]

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Bone, especially the spine, is the most frequently involved sites in NPC metastases, with an estimated incidence rate of 54–80%.[7,10-12] As reported, the median OS of patients with spinal metastasis is reported to be 12–23.5 months,[13–17] much shorter than those without spinal involvement. Obviously, spine involvement indicated a relatively poor prognosis for NPC patients. Though NPC is highly chemosensitive and radiation-sensitive, we found that disease control in some patients with spinal metastases of nasopharyngeal carcinoma (SMNPC) was not satisfactory with the use of chemotherapy, radiotherapy or combination of both. Usually, surgical interventions for SMNPC are rarely applied and mainly
indicated for patients with neurological compression and whose life expectancy is at least 6 months.[17] However, there is no large series of studies focusing on the surgical interventions for SMNPC because of its rarity.

In this retrospective study, we investigated the surgical treatment outcomes of SMNPC, to identify prognostic factors and to provide possible references for this subgroup.

Materials and Methods

Patients and Data Collection

SMNPC were confirmed by analyzing their disease histories combined with imaging examinations or pathological examination at our institution from January 2005 to December 2017. Informed consent was obtained from all patients or their legal guardians. This research was approved by Ethics Committee of our hospital. Tumor history, general condition (Karnofsky performance scale KPS), metastasis interval time (MIT, interval between the date of NPC diagnosis and the date of diagnosis with SMNPC), number of extraspinal bone metastases, number of vertebral metastases and visceral metastases, pathologic type, preoperative and postoperative neurological assessment based on the Frankel score,[18] treatment modality, surgery-related and the prognosis data were collected. In addition, serum lactic dehydrogenase (S-LDH), serum alkaline phosphatase (S-ALP) and hemoglobin levels before treatment were collected as well for prognosis analysis.

All patients were followed up on an outpatient basis at a 3-month interval in the first 6 months, and then at a 6-month interval for the remaining time. All patients were followed-up until death or the end of this study.

Criteria for Surgery

The surgical indications for SMNPC were as follows: (1) pathological fracture, or (2) spinal cord compression, or (3) continuous pain after conservative therapies such as drugs, chemotherapy and radiotherapy, and (4) Tomita score <8.[19] Surgical strategies were mainly made according to the Tomita score system, which is recommended widely for spinal metastases.[19–21]

Statistical Analysis

Survival analysis was performed with SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA). The postoperative OS was estimated by the Kaplan–Meier method, and univariate analysis for various possible prognostic factors (including age, sex, tumor type, KPS, preoperative Frankel score, spine involvement, number of metastases (multiple vs single), number of metastatic sites (more than one vs one), number of visceral metastases, MIT, treatment modality of the spine metastatic tumors, Hb, S-LDH and S-ALP level and Ki67) was performed by Log rank test. Factors with a P value ≤0.10 in univariate analysis were subjected to multivariate analysis Cox proportional hazards analysis. P values ≤0.05 were considered statistically significant.

Results

Patients' Characteristics

A total of 42 SMNPC patients were recorded between January 2005 and December 2017. Three patients who refused treatment or discontinued treatment halfway and 1 patient lost to follow up were excluded from this study. As the study focused on the surgical outcomes in SMNPC, eight other patients treated with adjuvant therapies were excluded as well. Finally, 30 patients treated with surgery were included and analyzed (Figure 1).

The details of the patients' demographic and clinical characteristics, and treatment approaches are presented in Table 1. The median age was 46.33 years (range: 30–70 years). Overall, 24 patients (80%) were male and 6 (20%) were female; 6 (20%) suffered synchronous metastasis, and 24 (80%) had asynchronous metastasis. The median MIT was 25.63 months (range from 0 to 120 months). No or a single visceral metastasis was found in 9 patients (30%) respectively, while multiple visceral metastases were found in 12 cases (40%). Single and multiple spine metastasis occurred in 15 patients each (50%). The most frequent site of vertebral metastasis was the thoracic spine

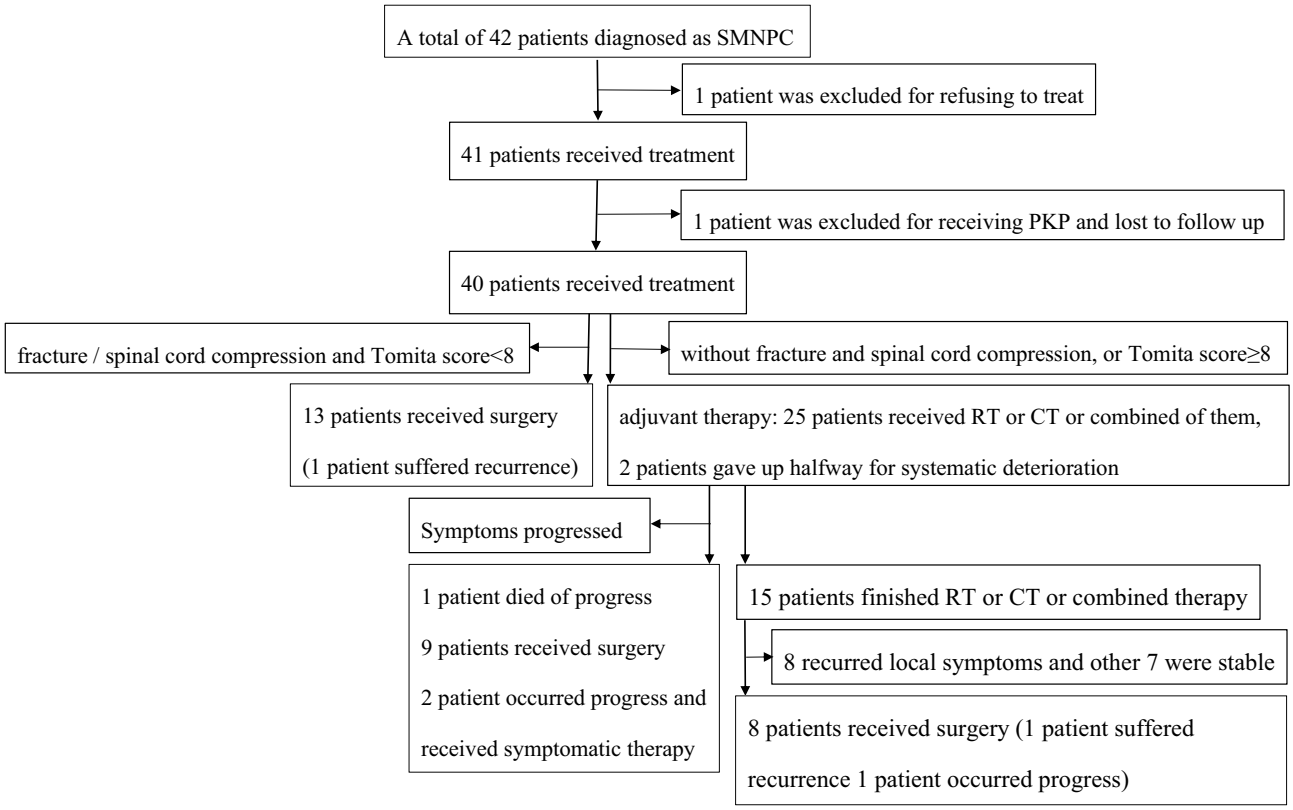

Figure 1 The patients flow diagram.

(17 cases, 56.67%), followed by the lumbar spine and cervical spine. Twenty-one (70%) patients had visceral metastases at admission while 17 (56.67%) were in good general condition according to the Karnofsky Performance Scale (KPS≥80). Histologically, 17 patients were classified as differentiated type, and the remaining 13 were undifferentiated.

Hemoglobin (Hb) less than 11 g/dL was found in only 4 cases, and the others had Hb levels of more than 11 g/dL. An albumin level (ALB) less than 40 g/L was found in 17 cases, while other patients were more than 40 g/L. The lactate dehydrogenase (LDH) level in 24 (80%) patients was more than 245 IU/L. Alkaline phosphatase (ALP) of the 22 (73.33%) was less than 110 (IU/L). Ki67 of the tumors was less than 30% in 10 and the others' were greater than 30% (Table 1).

Surgical Treatment of SMNPC

All 30 patients were treated with surgical interventions, combined with specific adjuvant therapies including chemotherapy, radiotherapy and zoledronic acid. Specifically, 13 patients received surgical interventions directly for pathological fracture and spinal cord compression, and the other 17 patients received surgical interventions after failure of adjuvant therapies. As a result, 9 patients (30%) received total en bloc spondylectomy (Figure 2), 11 patients (36.67%) received total piecemeal resection, and 10 (33.33%) received debulking or subtotal resection (Table 1). The average blood loss was 1488.89 mL, 1554.55 mL, and 757 mL in the en bloc, piecemeal and debulking group, respectively, and the average operation time was 327.22 mins, 311.36 mins and 195 mins, respectively. Additionally, all patients received local radiotherapy for primary and metastatic tumors before or after surgical treatment, and most of them (except in 3 cases) received systematic chemotherapy. Moreover, all the patients received bisphosphonates every month for the first year and every two months for the second year to avoid bone-related events.

Survival

At the last follow-up, two recurrences occurred in the piecemeal group and three cases of local progression occurred in the debulking group after the initial operation. However, secondary spinal cord compression was not detected in these five cases. The use of integrated therapies

Table 1 Demographic and Clinical Characteristics of the Series (n=30)

Characteristics	Number of Cases (%)
Gender	
Male	24 (80)
Female	6 (20)
Age at admission (yr)	Mean (46)
≤46	14 (46.67)
>46	16 (53.33)
Pathology type	
Differentiated	17 (56.67)
Undifferentiated	13 (43.33)
Preoperative KPS	
<80	13 (43.33)
≥80	17 (56.67)
Number of visceral metastasis	
None	9 (30)
Single	9 (30)
Multiple	12 (40)
Metastatic level of spine	
Cervical	6 (20)
Thoracic	17 (56.67)
Lumbar	6 (20)
Sacrum	1 (3.33)
Number of spine metastasis	
Single	15 (50)
Multiple	15 (50)
MIT (months)	
<12	14 (46.67)
≥12	16 (53.33)
Hb (g/dL)	
<11	4 (13.33)
≥11	26 (86.67)
ALB (g/L)	
<40	17 (56.67)
≥40	13 (43.33)
LDH (IU/L)	
<245	24 (80)
≥245	6 (20)
ALP (IU/L)	
<110	22 (73.33)
≥110	8 (26.67)
Ki67	
<30%	10 (33.33)
≥30%	20 (66.67)
Treatment	
E+A	9 (30)
P+A	11 (36.67)
D+A	10 (33.33)

Abbreviations: KPS, Karnofsky's performance scale; MIT, metastasis interval time; Hb, hemoglobin; ALB, albumin; LDH, lactic dehydrogenase; ALP, alkaline phosphatase; E, en bloc; P, piecemeal; D, debulking; A, adjuvant therapy.

and blockage function of the bone cement in front of the spinal cord might be the main reasons for these findings. Ultimately, 19 deaths (63.33%) were recorded. The median OS was 20.26 (range: 4–141) months after operation (Figure 3). The median survival was 34.11, 16.82, 11.6 months in the en bloc, piecemeal and debulking group, respectively. Regarding perioperative complications, one patient suffered from obvious leakage of cerebrospinal fluid and another with a sacral lesion experienced delayed wound healing in the piecemeal group.

Table 2 shows the prognostic values of specific parameters according to the univariate and multivariate Cox regression analyses. The univariate analyses revealed that preoperative KPS (p=0.0749), preoperative Frankel score (p=0.0037), number of visceral metastasis (p=0.0182), number of spine metastasis (p=0.0257), Ki67 (p=0.09) and treatment pattern (p=0.0254) were statistically significant. In multivariate analysis, adjusting for variables which were significant in univariate analysis, preoperative Frankel score (p=0.0094), number of visceral metastasis (p=0.015) and treatment pattern (p=0.029) were independent significant factors associated with survival (Figures 4–6).

Other clinical characteristics and laboratory factors (Hb, ALB, LDH, and ALP) were analyzed but were not found to have prognostic value for SMNPC.

Discussion

Necessity of Surgical Treatment for SMNPC

Nasopharyngeal cancer (NPC) is predominantly found in southern China. Bone has been thought to be the most common site of metastasis, with an estimated incidence rate of 70–80%.[22] NPC is highly radiosensitive, and radiotherapy is the mainstay of treatment for NPC, with a 95%

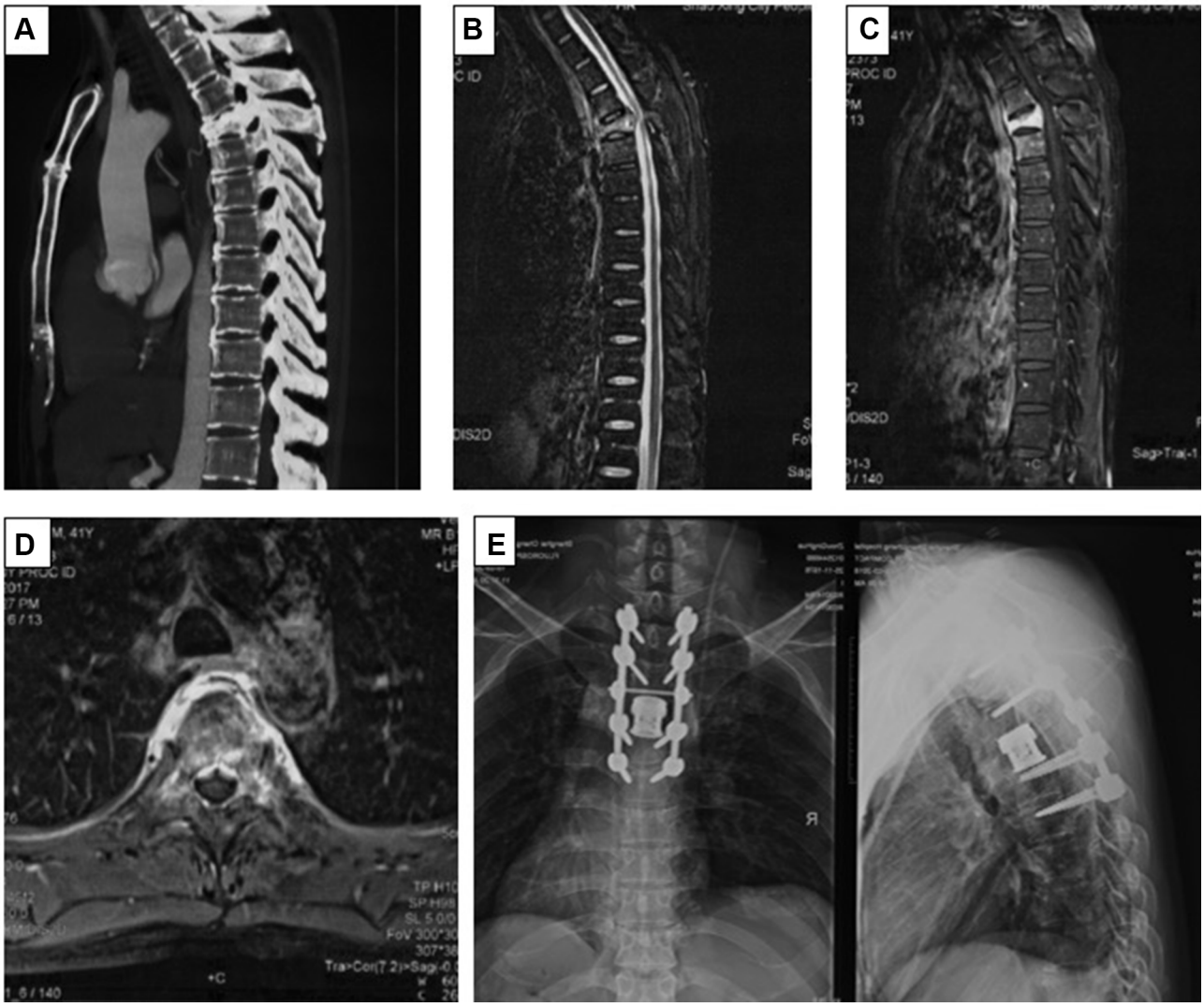

Figure 2 An illustrated SMNPC of total en bloc spondylectomy. (**A**) CT revealed compressed fracture at T4; (**B**–**D**) spinal cord compression and compressed T4 vertebra could be observed on MRI; (**E**) postoperative X-ray revealed total en bloc spondylectomy of T4 NPC and reconstruction.
Abbreviations: SMNPC, spinal metastases of nasopharyngeal carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.

5-year overall survival. NPC is also highly chemosensitive and platinum-based chemotherapy is the first-line treatment in patients with metastatic NPC.[15,16] However, we found that chemo-radiotherapy for SMNPC may fail though the primary lesions were controlled well. Shen et al[15] found that in NPC patients with bone-only metastases, spine involvement was a strong predictor for unfavorable OS ($p<0.05$). Similarly, by studying a large series of bone-only metastasis of NPC, Lu et al[16] and Kumar[17] also reported that vertebral metastasis was a significant prognostic factor ($p<0.01$). They also found that the more the spine involvement was, the poorer the prognoses. The reasons may lie in the corresponding complications (movement disorder, paralysis, secondary infection, urination and defecation function disturbance, etc.) of adjuvant therapy failure, followed by shorter survival. Hence, effective treatments for SMNPC are crucial once the failure of radiotherapy and chemotherapy occurs.

Our Experience

All 30 cases underwent a one-stage operation successfully. Reconstructions were mainly conducted with the combination of titanium cage, artificial vertebra or bone cement and rods-screws system. No failure of internal fixation happened. Among them, 17 patients (9 before and 8 after the completion of chemotherapy, radiotherapy or a combination of both, respectively) had to receive surgical interventions due to the disease progression (Figure 1).

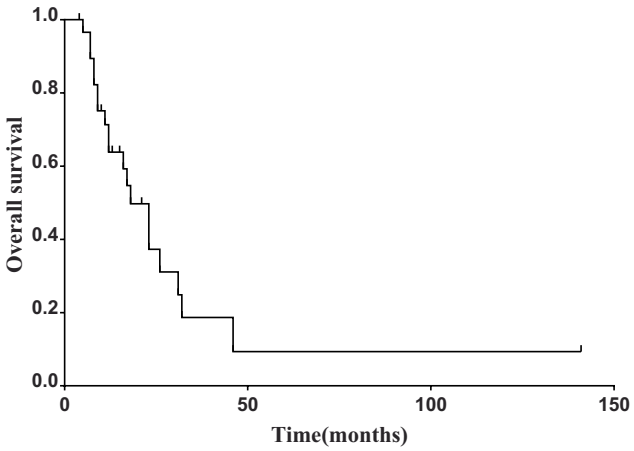

Figure 3 Kaplan–Meier plot showing overall survival of the 30 cases of SMNPC.

Radiotherapy or chemotherapy is not always that effective in the treatment of SMNPC though the high sensitivity to NPC. Surgical interventions were adopted for the goal of saving the neurological function or avoiding neurological deterioration, and prolonging the life expectancy. However, except for some limited mention,[17,23] no report of large series specifically focusing on the surgical treatment outcomes of SMNPC was found. The present study is the first one that focused on this issue.

As shown in the results, the surgical treatments for SMNPC were safe and the risks were limited and controllable with the updated surgical techniques. For the patients with cerebrospinal fluid leakage, the drainage was removed after controlled drainage without use of lumbar cerebrospinal fluid drainage since the intraoperative suture of dural sac was made. Another patient suffered delayed wound healing, which may have been due to the limited blood supply at the sacrum and the radiotherapy and chemotherapy he received. For the realities and reasons mentioned above, we prefer early surgical interventions for SMNPC patients when conservative therapies seem to be ineffective.

Prognostic Value of Different Elements

Value of Epidemiological Elements

In this study, the patients' median age (46.33 years) was nearly the same as that in previous reports of bone-only metastatic NPC.[15,17,24] Thus, the series were further divided into two groups (≤46 and >46 years) for further analysis. The male: female ratio was 4:1, indicating a male predominance of SMNPC, which was likely a result of the male predominance in NPC.[15,25] The prognostic value of age and sex was insignificant (p>0.1).

As reported, type III NPC has a better prognosis than type I and type II due to its high sensitivity to radiotherapy.[17,27] Among our SMNPC cases, type III accounted for 43.33% (13 cases), which is much low than the previously reported 95%.[26] According to the statistical analysis, the prognostic value of the pathology type (differentiated vs undifferentiated) was insignificant as well. This pathological difference may have led to the lower radiosensitivity of SMNPC in our study than that has been reported in other studies.

Regarding metastatic onset, Shen et al[15] reported that 43.9% were synchronous and 56.1% were asynchronous in their study of 312 bone-only metastatic NPCs. In this study, 6 (20%) metastases were synchronous and the other 24 (80%) were asynchronous, which is quite different from that of Shen's report. The median MIT was 25.63 months, a relatively long interval. Published literature has shown that MIT (≤24 vs >24 months or ≤12 vs >12 months) was a significant prognostic factor (p <0.01) for bone metastatic NPC.[16,25,28,29] Nevertheless, this was not confirmed in our SMNPC series.

Value of Serum Parameters

Elevated LDH is frequently observed in cancer patients.[30] According to previous literature, NPC patients with abnormally elevated LDH had significantly worse outcome compared with those who had normal LDH level.[31,32] Similarly, previous researchers found that Hb <11.0 g/dL, ALB <40 g/L, and LDH ≥245 IU/L implied poor prognosis in bone-only metastatic NPCs.[16,29] In another report, ALP (≤110 vs >110 IU/L) appeared to be a significant independent prognostic index in patients with skeletal metastatic NPC.[33] Nevertheless, no prognostic value was discovered among these above factors in our SMNPC patients.

Potential Prognostic Factors

Similar to other spine metastatic tumors,[24,28] the thoracic spine had been reported to be the most frequent site of SMNPC. Furthermore, patients with metastases involving the spine had strikingly poor OS. Notably, those with more than three metastases in the spine had especially poor prognosis.[15,17] In the current study, univariate analysis also showed that the number of spine metastasis (single vs multiple) was a potential predictor for unfavorable OS among patients with SMNPC (p=0.0376), but it was not an independent factor after the multivariate analysis.

The majority of the researchers[15,17] believed that the KPS was significant for predicting prognosis in cancer

Table 2 Univariate and Multivariate Analysis of Variables for SMNPC

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender Male vs Female	1.749(0.603, 5.067)	0.303		
Age (yrs) ≤46 vs >46	1.464(0.590, 3.632)	0.411		
Pathology type Di vs UD	1.936(0.745, 5.033)	0.175		
Preoperative KPS <80 vs ≥80	2.231(1.889, 5.600)	0.0874		
Preoperative FS A,B,C/D,E	4.681(1.461, 14.993)	0.0094	4.68(1.461–14.99)	0.0094*
Visceral metastasis N vs S vs M	2.664(1.277, 5.559)	0.009	2.58(1.203–5.544)	0.015*
Metastatic level C vs T vs L	0.899(0.496, 1.627)	0.725		
Count of SMNPC S vs M	3.185(1.074, 9.444)	0.0367		
MIT <12 vs ≥12	1.944(0.680, 5.558)	0.215		
Hb (g/dL) <11 vs ≥11	2.404(0.528, 10.94)	0.257		
ALB (g/L) <40 vs ≥40	1.377(0.480, 3.955)	0.552		
LDH (IU/L) <245 vs ≥245	1.461(0.461, 4.628)	0.519		
ALP (IU/L) <110 vs ≥110	1.204(0.425, 3.414)	0.727		
Ki67 <30% vs ≥30%	2.688(1.770, 9.378)	0.0900		
Surgical option E vs P vs D/S	2.274(1.209, 4.276)	0.0108	2.31(1.136–6.421)	0.029*

Note: *Indicated statistical significance (P values ≤ 0.05).

Abbreviations: Di, differentiated; UD, undifferentiated; KPS, Karnofsky's performance scale; FS, Frankel score; N, none; S, single; M, multiple; C, cervical; T, thoracic; L, lumbar; SMNPC, spinal metastases of nasopharyngeal carcinoma; MIT, metastasis interval time; Hb, hemoglobin; ALB, albumin; LDH, lactic dehydrogenase; ALP, alkaline phosphatase; E, total en bloc; P, total piecemeal; D/S, debulking/subtotal.

patients. However, this may not be true for all.[28] In a study including 80 bone-only metastatic NPC patients, Lu et al[16] found no prognostic value of the KPS. In our study, in the univariate analysis, patients with a preoperative KPS ≥80 tended to have a longer survival than those with a preoperative KPS < 80 (24 months vs 15 months, p=0.0874), while the multivariate analysis results did not reveal significance.

Ki67 is an excellent marker of cell proliferation,[34,35] and higher Ki67 expression has been found to be associated with poor OS and disease-free survival in NPC.[26] We divided the SMNPC patients into two groups according to the Ki67 value and found that the group with Ki67 <30% had a better prognosis than the group with Ki67 ≥30% (univariate analyses p=0.09). However, Ki67 did not indicate significantly predictive power in the multivariate analysis.

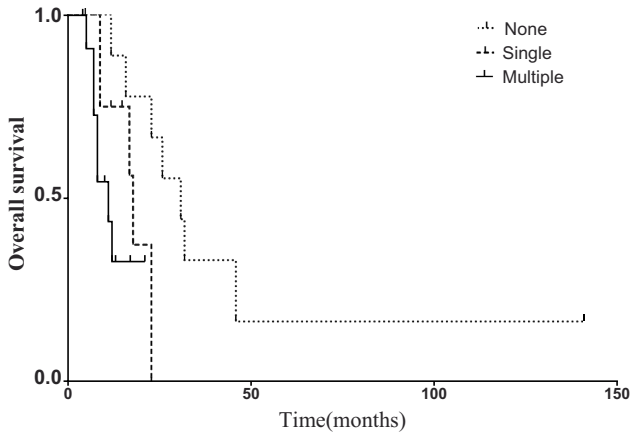

Figure 4 Kaplan–Meier curve for visceral metastasis (None/Single/Multiple).

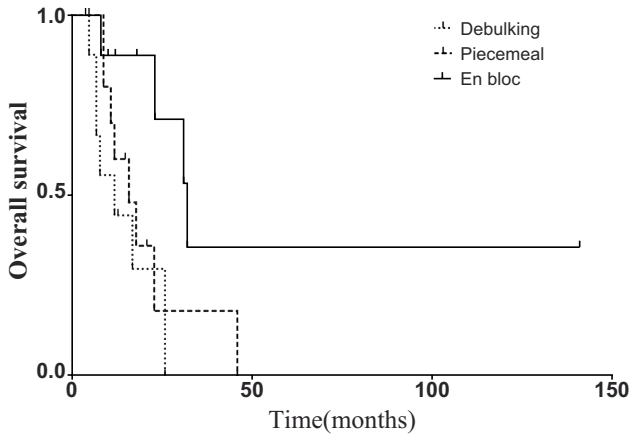

Figure 6 Kaplan–Meier curve for surgical option (En bloc/Total piecemeal/debulking or subtotal).

Independent Prognostic Factors

Visceral metastasis is important for determining the treatment and prognosis of patients with malignant tumors according to the Tokuhashi score, Tomita score and other literature focused on spine metastases from varied malignant tumors.[17,19,36] The reason lies in that visceral metastasis indicates a poor systemic status, usually a terminal stage. Additionally, the Frankel score has been broadly accepted as a useful tool to evaluate the neurological function as well as a predictor for late recovery.[36,37] Remarkably, preoperative Frankel score and the number of visceral metastasis were found to be independent prognostic factors for SMNPC after univariate analysis and multivariate analysis, in accordance with previous studies (Table 2, Figures 4 and 5).

Another independent prognostic factor of SMNPC was the surgical mode. Presently, total en bloc spondylectomy (TES) has been increasingly recognized, and widely accepted for the treatment of specific spine tumors and has better tumor control than piecemeal and subtotal resection.[38,39] In our series, the resection mode included total en bloc spondylectomy, total piecemeal spondylectomy and debulking or subtotal resection, which technique to use was mainly based on the Tomita classification and WBB staging. The final statistical results revealed that TES resulted in better OS than those treated with piecemeal and subtotal mode (p=0.029, 95% CI 1.136–6.421, Figure 6). Since TES is a common and well-developed method for spine tumor therapy, we strongly recommend it when possible for appropriate patients.

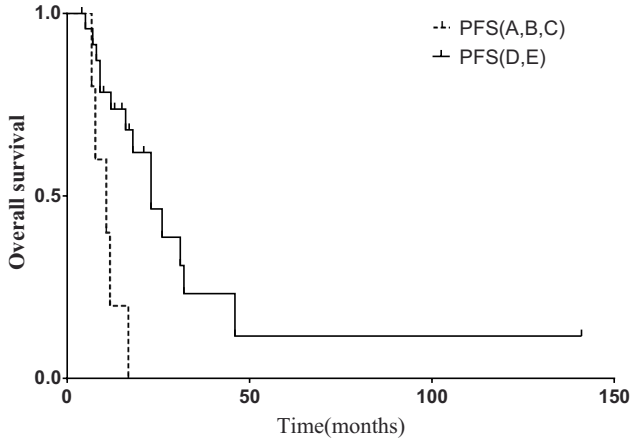

Figure 5 Kaplan–Meier curve for preoperative FS (A, B, C/D, E).
Abbreviation: FS, Frankel score.

Limitations

Several limitations should be addressed for our series. First is the retrospective nature of the study. Second, our results were concluded from a relatively small sample from a single institution due to the great rarity of SMNPC. Finally, the adjuvant therapies were heterogeneous, which might have a confounding effect. We believe that further studies with large samples and great consistency are needed.

Conclusions

We report the first study aimed at SMNPC and its surgical treatment, and provide several notable findings. The thoracic spine was the most frequently involved level of SMNPC, while a pathological type predominance was not observed in our series. In addition, preoperative Frankel score, number of visceral metastasis and surgical resection mode may be independent prognostic factors for SMNPC. Combined with chemotherapy and radiation, surgical interventions should be recommended when necessary.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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