

## Prevalence of Known and Unknown Primary Tumor Sites In Spinal Metastasis Patients

Permsak Paholpak\*, Winai Sirichativapee, Taweechok Wisanuyotin, Weerachai Kosuwon and Polasak Jeeravipoolvarn

Department of Orthopedics, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand

**Abstract:** *Study Design:* A retrospective study.

*Objectives:* Three objectives have been designated for this study: (1) to determine the prevalence of identifiable and non-identifiable primary tumor sites in patients with spinal metastasis, (2) to identify the most common site of the known primary tumor sites, and (3) to identify the factors associated with survival time.

*Summary of Background Data:* The spine is the third most common metastatic site for several primary visceral carcinomas. The primary tumor site could not be identified in 15% to 20% of patients who had been diagnosed of with a skeletal metastasis. Most of the previous studies on skeletal metastasis have not been limited to spinal metastasis alone.

*Methods:* Between January 2007 and July 2011 reviews were done for 82 patients with spinal metastasis who had not received a previous diagnosis of carcinoma. The assessment parameters included the following: general demographic data, Karnofsky score, Frankel score, number of spinal vertebra affected, region of the spine affected by metastasis, other skeletal metastasis site, visceral metastasis, known or unknown primary sites of metastasis, histological cell type of metastasis, and the survival period. The log-rank test and Cox proportional hazard model were used to study the survival analysis.

*Results:* Of the 82 patients included in the study, 56 were male. The mean age was 57 years. 86.6% had a known primary carcinoma site while the remaining 13.4% had none. The two most common known carcinoma sites were the lung and biliary systems. Among the 11 unknown primary sites, the most common histological finding was adenocarcinoma. The mean survival period was  $8.7 \pm 11.7$  months. The survival analysis revealed two statistically significant factors: *the primary tumor site's aggressiveness* ( $P < 0.005$ ) and *the presence of visceral metastasis* ( $P < 0.05$ ).

*Conclusion:* The prevalence of identifiable primary site was 86.6% and the most common site was the lungs followed by the biliary system. The *primary carcinoma site's aggressiveness* and *the presence of visceral metastasis* were the factors associated with patient survival.

**Keywords:** Spinal metastasis, known primary tumor, unknown primary tumor, cholangiocarcinoma, survival analysis.

### INTRODUCTION

Metastatic carcinoma is one of the leading causes of death around the world. In metastatic patients, a period of prolonged survival is likely to result in an increasing incidence of spinal metastasis [1].

The skeletal system is the third most common site for metastasis, and the most common sites are the lung and liver, respectively. In the skeletal system, the spine is the most commonly affected part [1, 2] with the thoracic area most commonly involved followed by the cervical and lumbar areas [3]. By the time of initial presentation and diagnosis, usually the spinal metastasis already involves more than two vertebrae [1].

The most commonly identified primary sites for carcinoma in spinal metastatic patients are the lungs, breasts,

the prostate, kidneys and the hematopoietic system [4-8]. Only 80-85% of primary carcinoma sites were identifiable, according to Rougraff *et al.*, even after performing a thorough investigation (including a careful history and physical examination, standard laboratory tests, CXR, CT chest and abdomen  $\pm$  pelvis, and Tc-99m bone scan). After performing an additional transpedicular biopsy at the affected vertebral level, an additional 8% of the primary carcinoma sites were identifiable [1, 4].

Many studies reported the type of primary tumor was one of the most powerful prognostic factors [1, 5-13]. The identification of the primary tumor type was very helpful in selecting the best treatment option for the patients [10]. Beside the primary tumor histology, the survival prognosis for spinal metastatic patients is influenced by many factors, including: overall functional status, neurological status, and the overall burden of the diseases [1, 9].

Our facility, Khon Kaen University Hospital, is a referral hospital centrally located in Northeastern Thailand. This region of Thailand is considered an endemic area for

\*Address correspondence to this author at the Department of Orthopedics, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand; Tel: +6643-348398; Fax: +6643-348-398; E-mails: [permpa@kku.ac.th](mailto:permpa@kku.ac.th), [paholpak@yahoo.com](mailto:paholpak@yahoo.com)

cholangiocarcinomas, the bile duct epithelium neoplasm. The prognosis of the cholangiocarcinoma patients is extremely poor [14-17]. However, the prevalence of this carcinoma in patients who have come to our hospital with spinal metastasis is not well understood. This lack of understanding has lead us to perform this study.

The aims of our study were established as follows: (1) to assess the prevalence of known and unknown primary carcinoma sites among patients with spinal metastasis, (2) to identify the five most common primary carcinoma sites at our hospital, and (3) to identify the factors that influence survival.

## MATERIALS AND METHODS

We retrospectively reviewed all of the patients that presented with spinal metastasis at Srinagarind Hospital at Khon Kaen University between January 2007 and July 2011. In total, 136 patients having been diagnosed with spinal metastasis were enrolled. Patients were included in the study only if they had been evaluated in accordance with all of following investigation parameters: (a) standard history and physical examination, (b) standard laboratory investigation including tumor markers (CEA, AFP, PSA,  $\pm$  CA125), (c) TC-99m bone scan, (d) CT of chest abdomen  $\pm$  pelvis, (e) plain film of the affected spinal level, (f) an MRI of the spine at least showing the affected region, and (g) a biopsy at the affected vertebral level. After considering these criteria, a total of 82 have been included in our study.

We have recorded all of the parameters from the out-patient and in-patient record forms for all 82 of these patients. The recorded parameters were: general demographic data, performance status (Karnofsky score) [18], neurological status (Frankel score) [19], number of the spinal vertebra affected by metastasis, the region of the spine affected by metastasis, the presence or absence of other skeletal metastases, the presence or absence of visceral metastases, known or unknown primary sites of metastasis, histological cell types of metastases, and the survival period of the patients.

The data was analyzed for percentages and survival analyses were performed using the log-rank test and the Cox proportional hazard model. A P-value of  $< 0.05$  was considered statistically significant. SPSS for Windows version 15.0 was used for the statistical analyses.

## RESULTS

The demographic data is presented in Table 1. The demographic data indicated that spinal metastases occurred more frequently in males at our hospital. The mean performance status score was of an intermediate level ( $53.15 \pm 12.19$ ). About 41.46% of the patients presented with incomplete cord lesion (Frankel rating score = C). Most of the spinal metastasis patients came to the hospital with more than two levels of vertebral involvement. The most commonly affected region was the thoracic region and most of the patients presented with extra-skeletal and visceral metastases.

After following the investigative protocols, the primary carcinoma sites in 71 patients (86.6%) were able to be identified, but in 11 patients (13.4%) these sites were unable

to be identified. The rank of the five most commonly known sites were: the lungs, the biliary system, the hematologic system (excluding MM), the prostate, and the breasts, respectively (Table 2).

**Table 1. Demographic Data**

Demographic Data	
Age (Mean $\pm$ SD)	56.4 $\pm$ 12.19 (29-86)
• Male	58.75 $\pm$ 12.32
• Female	51.3 $\pm$ 10.45
Gender	
• Male	56(68.29%)
• Female	26
Kanofsky performance score(mean $\pm$ SD)	53.15 $\pm$ 16.35
Neurological involvement (Frankel scale)	
• A (Complete paraplegia)	12 (14.63%)
• B	8 (9.75%)
• C	31 (41.46%)
• D	16 (19.51%)
• E (Normal)	15 (18.29%)
No. of spinal metastases	
• 1 level	10 (12.19%)
• 2 levels	14 (17.07%)
• $\geq 3$ levels	58 (70.7%)
Affected spinal region	
• Cervical	26
• Thoracic	95
• Lumbar	38
No. of extraspinal skeletal metastases	
• 0	23 (28%)
• 1	3 (3.65%)
• 2	11 (13.41%)
• $\geq 3$	45 (54.87%)
No. of visceral metastases	54 (65.85%)

Regarding the unknown primary sites, the most common histological finding was that of adenocarcinoma followed by squamous cell carcinoma and neuroectodermal carcinoma (Table 2).

The mean survival period for spinal metastasis patients at our hospital was  $8.7 \pm 11.7$  months. About a third (28; 34.14%) of patients died during the 3 month period after the diagnosis, 13 (15.85%) lived more than 1 year, and only 7 (8.5%) survived more than 2 years.

The survival analysis, using the log-rank test (a univariate analysis) indicated that the *primary carcinoma site aggressiveness* was the only statistically significant factor (Table 3).

According to the multivariate survival analysis (using the Cox proportional hazard model) both '*presence of visceral metastasis*' and '*aggressiveness of the primary carcinoma site*' were the statistically significant factors (Table 4).

**Table 2. Primary Carcinoma Sites that could be Identified and Unidentified**

Primary Carcinoma Sites (N 82)	
<b>Known Primary Carcinoma Sites 71 (86.6%)</b>	
Lung	17(23.94%)
Cholangiocarcinoma	15(21.12%)
Hematogenous malignancy (excluding MM)	7(9.85%)
Prostate	6(8.45%)
Breast	5(7.04%)
Thyroid	3(4.22%)
MM	3(4.22%)
Cervix	3(4.22%)
Others (i.e. nasopharynx, rectum, ovary, liver)	12(16.90%)
<b>Unknown Primary Carcinoma Sites 11 (13.4%)</b>	
Adenocarcinoma	8(72.72%)
Squamous cell carcinoma	2(18.18%)
Neuroectodermal carcinoma	1(9.09%)

**Table 3. Univariate Survival Analysis Using the Log-Rank Test**

Univariate Analysis (Log-Rank Test)	P-Value
Karnofsky score [low(N15), intermediate (N44), high (N13) ]	0.463
No. of spinal metastases [1(N10), 2 (N14), ≥3 (N58)]	0.205
No. of extra-spinal metastases [0 (N23), 1-2(N14), ≥3 (N45)]	0.767
Visceral metastases (absent vs present)	0.594
Neurologic deficit [A-B (N20), C-D (N47), E (N31)]	0.650
Primary tumor [Score 0 (N17),1 (N35), 2 (N 17), 3 (N0), 4 (N1), 5 (N12)] [9,20]	0.008*
Primary tumor [Slow (N14), Moderate (N19), Rapid growth (N49)] [21]	0.002*

No. is number, N is number of patients, \*is statistically significant.

## DISCUSSION

Rougraff and colleagues were able to identify the primary carcinoma sites in nearly 90% of patients and rank the most commonly known primary sites which were the lungs, kidneys, liver, thyroid, breasts, colon and bladder [4]. Tang Xiao Dong *et al.* were able to identify the primary carcinoma sites in 70.5% and rank the five most commonly known primary sites which were the lungs, kidneys, prostate, liver and breasts [22].

In this study, the primary carcinoma sites in 86.6% were able to be identified, and the five most commonly identified primary sites were the lungs, the biliary system, the hematologic system (excluding MM), the prostate and the

breasts. Surprisingly, we found the biliary system to be among the five most commonly identifiable primary sites and not the kidneys. A large number of cholangiocarcinomas were found because this cancer is a very common type of biliary tract cancer, and the highest incidence of this cancer in the world is found here in Northeastern Thailand [14, 23].

In the survival analysis of this study, it was discovered that if the primary sites were more aggressive, the patients' survival period was shorter when compared to cases having less aggressive primary tumor sites. Additionally, if the patients also presented with visceral metastasis, their survival outcome was poorer.

The limitations of this study are as follows: (1) This study is a retrospective study and some problems may arise regarding the quality of the reported files. All collected patient data is as complete as possible and is derived from the scanned medical record files from the hospital's computer system for both in-patients and out-patients. (2) There were a small number of spinal metastasis patients which made it difficult to do the survival analysis (by type) using the Kaplan-Meier curve. (3) Because of the small numbers of each identified primary carcinoma site, it was also difficult to do the survival analysis (by type) using the Kaplan-Meier curve. (4) Due to the varied options for treatment which ranged from observation to surgical treatment during the 5 year period of data collection, the treatment modality for spinal metastasis might have affected patient survival. In regard to the treatment of spinal metastasis, this factor has not been considered in our study. (5) Because the results of a 'whole spine MRI' were not available for some of the patients, it is possible that other metastatic lesions were missed and not detected by the Tc-99m bone scan [24]. Furthermore, this study was performed between January 2007 and July 2011. During that period some techniques for assessing primary tumor sites in spinal metastasis were changed. For example, the advances in immunohistochemistry staining can now identify primary carcinoma sites more easily and accurately. Additionally, advances in CT and MRI may lead to earlier detection of tumors at their primary and metastatic sites. When compared to these advances, our facility still employs the same methodology today as was used in 2007 to assess the primary tumor sites in spinal metastasis patients.

## CONCLUSION

Our study shows that if the investigation protocols are followed and a biopsy is performed at the affected vertebral level, it is possible to identify 86.6% of primary sites of carcinoma. The most commonly identified primary site was the lungs followed by the biliary system (*viz.*, intrahepatic bile duct cancer or cholangiocarcinoma). Among the 13.4% of unknown primary carcinoma sites, adenocarcinoma was the most common pathological finding. Regarding the survival analysis, only aggressiveness of the primary carcinoma site and presence of visceral metastasis significantly affected the survival outcome.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

**Table 4. Multivariate Survival Analysis Using the Cox Proportional Hazard Model**

Multivariate Analysis (Cox Proportional Hazard Model)	HR	95% CI	P
Karnofsky score			0.886
(1) Intermediate vs low	1.417	0.355-5.997	0.636
(2) High vs Intermediate	1.218	0.350-4.239	0.756
No. of spinal metastases(Solitary vs Multiple)	0.304	0.336-2.580	0.275
No. of extraspinal metastases(absence vs presence)	1.058	0.465-2.404	0.893
Visceral metastases (absence vs presence)	2.264	1.041-4.922	0.039*
Neurologic deficit(Frankel scale)			0.955
(1) A-B vs C-D	1.284	0.204-8.071	0.790
(2) E vs C-D	1.089	0.294-4.026	0.899
Primary tumor			0.009*
(1) Moderate vs slow	0.206	0.075-0.566	0.002*
(2) Rapid vs moderate	0.712	0.286-1.772	0.465
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