RESEARCH ARTICLE

Prevalence and Survival Patterns of Patients with Bone Metastasis from Common Cancers in Thailand

Areerak Phanphaisarn[1,2], Jayantorn Patumanond[1], Jongkolnee Settakorn[3], Parunya Chaiyawat[3], Jeerawan Klangjorhor[3], Dumnoensun Pruksakorn[3,4]*

Abstract

Background: Bone metastasis is a single condition but presents with various patterns and severities. Skeletal-related events (SREs) deteriorate overall performance status and reduce quality of life. However, guidelines for early detection and management are limited. This study includes a survey of the prevalence of bone metastasis in cases with common cancers in Thailand as well as a focus on survival patterns and SREs. Materials and Methods: A retrospective cohort analysis was conducted using a database of the Chiang Mai Cancer Registry and the Musculoskeletal Tumor Registry of the OLARN Center, Chiang Mai University. The prevalence of bone metastasis from each type of primary cancer was noted and time-to-event analysis was performed to estimate cancer survival rates after bone metastasis. Results: There were 29,447 cases of the ten most common cancers in Thailand, accounting for 82.2% of the entire cancer registry entries during the study period. Among those cases, there were 2,263 with bone metastases, accounting for 7.68% of entries. Bone metastasis from lung, liver, breast, cervix and prostate are common in the Thai population, accounting for 83.4% of all positive cases. The median survival time of all was 6 months. Of the bone metastases, 48.9% required therapeutic intervention, including treatment of spinal cord and nerve root compression, pathological fractures, and bone pain. Conclusions: The frequency of the top five types of bone metastasis in Thailand were different from the frequencies in other countries, but corresponded to the relative prevalence of the cancers in Thailand and osteophilic properties of each cancer. The results of this study support the establishment of country specific guidelines for primary cancer identification with skeletal lesions of unknown origin. In addition, further clinical studies of the top five bone metastases should be performed to develop guidelines for optimal patient management during palliative care.

Keywords: Bone metastasis - prevalence - survival rate - skeletal-related events - Thailand

Asian Pac J Cancer Prev, **17 (9)**, 4335-4340

Introduction

Bone is a common site for cancer metastasis. Skeletal-related events (SREs) deteriorated overall performance and reduced quality of life, although it is not a direct cause of death. Early detection of bone metastasis could decrease skeletal complications through timely prophylactic surgery or bone-targeted agents (Coleman, 2006). However, there have been only limited guidelines published on early detection and management of metastasis. Screening for bone metastasis is not currently recommended for all types of primary cancer. Some bone metastases, e.g., rapidly progressive cancers including lung cancer, can be concomitantly found before the primary site diagnosis has been accomplished (Nguyen et al., 2009). However, bone metastasis in slow, progressive cancers can present with complications (uncorrectable in some cases) because of a lack of effective screening procedures. Furthermore, urgent complications, including spinal cord compression and pathological fractures, might not be able to be treated immediately without an

The decision to perform invasive intervention is not dependent exclusively on clinical events: survival expectancy should also be taken into consideration. Survival period, in turn, is determined by different factors including the type of primary cancer and the accessibility of treatment. Bone metastases from different types of primary cancers present with different patterns. For example, those from well-differentiated thyroid cancers present with a very good prognosis and deserve to receive surgical interventions (Qiu et al., 2011; Sugino et al., 2014), while a rapidly progressive cancer including lung cancer might not be improved the overall performance with surgical interventions (Tomita et al., 2001). Breast

*[1]Department of Clinical Epidemiology, Faculty of Medicine, Thammasat University, [2]Department of Orthopedics, [3]Orthopedic Laboratory and Research Netting Center (OLARN Center), Department of Orthopedics, [4]Excellence Center in Osteology Research and Training Center (ORTC), [5]Department of Pathology, Faculty of Medicine, Chiang Mai University, Thailand *For correspondence: dumnoensun.p@cmu.ac.th*

cancer with bone metastasis presents a better prognosis compared with other sites of distant metastasis. The long survival period might be expected to found the second and third SREs (McDougall et al., 2016; Tanaka et al., 2016).

In addition to the biology of the disease, the prevalence of primary cancer is an important factor in determining the number of bone metastases. The prevalence of primary cancers varies among different countries as it depends on the genetic background of the population as well as local environmental exposure. Knowing the common types of primary cancer-caused bone metastases in Thailand would be an important step in developing treatment guidelines. In this study, the prevalence of bone metastasis in Chiang Mai University Hospital was surveyed and the survival patterns of common types of cancer with bone metastasis and SREs were determined.

Materials and Methods

Data sources

Retrospective cohort analysis was performed of the ten most common cancers in Thailand using data obtained from the Chiang Mai Cancer Registry, Chiang Mai University Hospital, for the period 1 January 2006 through 31 Dec 2015. Chiang Mai University Hospital is a tertiary center, caring for cancer patients in the northern region of Thailand. The ten leading cancers included lung cancer (ICD-O-C34), liver cancer (ICD-O-C22), cervical cancer (ICD-O-C53), breast cancer (ICD-O-C50), rectal cancer (ICD-O-C20), colon cancer (ICD-O-C18), thyroid cancer (ICD-O-C73), stomach cancer (ICD-O-C16), urinary bladder cancer (ICD-O-C67) and prostate cancer (ICD-O-C61). Data on bone metastasis was also obtained from cancer registry for ICD-O-primary.2 metastasis cases. Related clinical courses of treatment, including skeletal-related events and bone metastases, were obtained from the Medical Records Liberian and Statistic, Faculty of Medicine, Chiang Mai University. Records of bone metastasis and skeletal-related events were sorted by ICD-10 secondary malignant neoplasm of bone (C795), pathological fracture secondary from cancer (M809), spinal cord compression (G952), palliative care (Z515), ICD-9 code (surgery for bone metastasis), decompressive laminectomy (0309), and radiation procedures (92.24 and 92.29). Survival data was retrieved using the patients' identification number from the Civil Registration Database of the Thai Ministry of the Interior. Data on SREs and interventions of bone metastasis was collected from the Musculoskeletal Tumor Registration records of the OLARN Center, Department of Orthopedics, for the period 1 Jan 2011 through 31 Dec 2015. This study was approved by Ethics committee of the Faculty of Medicine, Chiang Mai University (EC-ORT-2558-03557).

Statistical Analysis

Time-to-event analysis was performed using a Kaplan-Meier curve to estimate median survival time and overall survival rate of cancer patients after bone metastasis.

Results

Demographic data of the ten most common cancers with bone metastasis in Thailand

From the Chiang Mai Cancer Registry a total of 35,838 of cancer cases were identified during the study period. From that list, the ten most common cancers following the sequential order of the country database were extracted, a total of 29,447 cases accounting for 82.2% of all cases in the cancer registry. The demographic data of the cancer cases is shown in Table 1. There were 2,263 bone metastasis cases accounting for 7.68% of the cohort. Prevalence and age distribution data of the bone metastases is shown in Figure 2. One third of the bone metastases (35.2%) found in clinical practice occurred from lung cancer, and 83.4% of the bone metastases originated from one of the five most common primary cancers: lung, liver, breast, cervix and prostate. The mean age of bone metastasis occurrence was 58.9 years (range 46.1-71.7). There was a high prevalence of bone metastasis from cancer of the breast, cervix and rectum in individuals under 55 years old; a high prevalence of bone metastasis from cancer of the liver, thyroid, colon and stomach in those aged between 56 and 60, and a high prevalence of bone metastasis from cancer of the lung, prostate, and bladder in people over 60 years old. The ratio of bone metastases from each type of cancer, representing its osteophilic property, is shown in Figure 3. Prostate cancer was the most osteophilic, with the highest ratio of bone metastasis (21.5%).

Table 1. Demographic data on the ten most common cancers in Thailand (data collected from Chiang Mai Cancer Registry)

Cancer	ICD-10	Number	%	M: F	Age (mean±sd)		
					Over all	Male	Female
Lung	C34	7,455	25.3	2.3:1	62.6(±11.1)	62.9(±11.1)	62.2(±11.7)
Liver	C22	5,728	19.5	2.7:1	57.3(±12.0)	56.7(±11.9)	59.0(±12.1)
Cervix	C53	4,614	15.7	-	52.0(±12.1)	-	52.0(±12.1)
Breast	C50	4,050	13.7	0.02:1	52.2(±11.6)	57.0(±13.1)	52.1(±11.6)
Rectum	C20	1,658	5.6	1.3:1	59.9(±13.8)	57.9(±13.3)	59.1(±13.6)
Colon	C18	1,516	5.2	1.2:1	59.5(±14.0)	59.8(±14.1)	59.7(±14.1)
Thyroid	C73	1,417	4.8	0.28:1	47.7(±16.9)	51.8(16.9)	46.6(±16.7)
Stomach	C16	1,257	4.3	1.3:1	58.2(±14.0)	60.1(±13.6)	55.7(±14.2)
Urinary bladder	C67	1,037	3.5	3.0:1	66.4(±12.3)	66.7(±12.2)	65.4(±13.9)
Prostate	C61	715	2.4	-	70.2(±9.3)	70.2(±9.3)	-
Total	-	29,447	100	0.77:1	57.6(±13.4)	60.7(±12.6)	55.1(±13.4)

Table 2. Median Survival Time and Overall Survival Rate of Cancer Cases with Bone Metastasis

Cancer	Median survival time (month)	Overall survival (%)			
		3rd-month (95%CI)	6th-month (95%CI)	9th-month (95%CI)	12th-month (95%CI)
Stomach	2.6	46.7(28.4-63.0)	33.3(17.5-50.0)	26.2(12.2-42.7)	18.7(7.1-34.7)
Lung	2.8	48.1(44.4-51.6)	27.7(24.5-31.0)	15.7(13.1-18.4)	10.6(8.5-13.0)
Liver	4	60.6(55.8-65.1)	39.4(34.7-44.0)	26.7(22.6-31.0)	17.8(14.3-21.7)
Urinary bladder	6.5	67.0(56.7-75.4)	54.6(44.2-63.9)	41.2(31.4-50.8)	31.8(22.8-41.2)
Cervix	10.2	78.9(71.4-84.6)	66.7(58.5-73.6)	54.9(46.5-62.5)	46.6(38.3-54.4)
Breast	11.1	80.8(76.1-84.6)	67.6(62.2-72.4)	59.6(54.1-64.8)	48.3(42.7-53.7)
Colon	13.6	87.2(77.5-92.9)	72.9(61.5-81.4)	62.5(50.7-72.2)	55.9(44.2-66.2)
Rectum	16.3	91.3(81.7-96.0)	79.5(67.9-87.3)	69.2(56.8-78.7)	63.2(50.6-73.4)
Thyroid	17.2	84.1(75.4-89.9)	79.9(68.5-84.9)	69.7(59.9-77.8)	59.5(49.1-68.4)
Prostate	38.1	96.0(91.3-98.2)	89.8(83.7-93.7)	84.8(77.9-89.7)	78.8(71.0-84.7)
Overall	6	66.3(64.3-68-3)	49.9(47.8-52.0)	39.1(37.1-41.2)	31.5(29.5-33.5)

Table 3. Frequency of Skeletal-Related Events with Each Type of Primary Cancer

Primary cancer	Spinal cord compression	Pathological fracture	Bone pain*	Asymptomatic BM**
Lung cancer	68(41.2%)	56(46.7%)	213(55.6%)	277(37.1%)
Liver cancer	31(18.8%)	18(15.0%)	60(15.7%)	113(15.1%)
Breast	26(15.8%)	22(18.3%)	41(10.7%)	157(21.0%)
Cervix	14(8.5%)	5(4.2%)	20(5.2%)	74(9.9%)
Prostate	12(7.3%)	8(6.6%)	17(4.4%)	30(4.0%)
Others	14(8.4%)	11(9.2%)	32(8.4%)	96(12.9%)
Total (1,415)	165(100%)	120(100%)	383(100%)	747(100%)

*Bone pain which require surgery, or radiation, **No intervention for treatment of bone metastasis

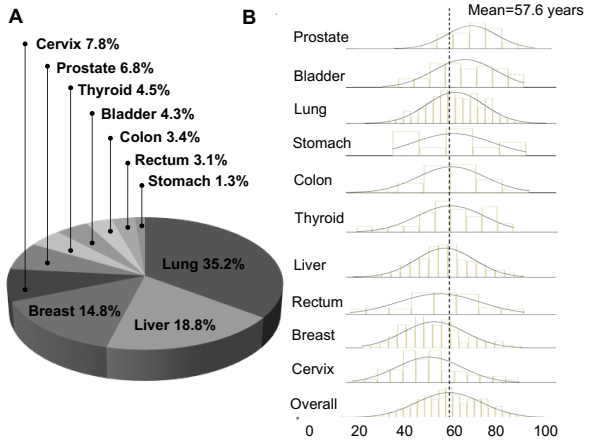

Figure 1. Prevalence and Age Distribution of Bone Metastasis with the Ten Most Common Cancers in Thailand

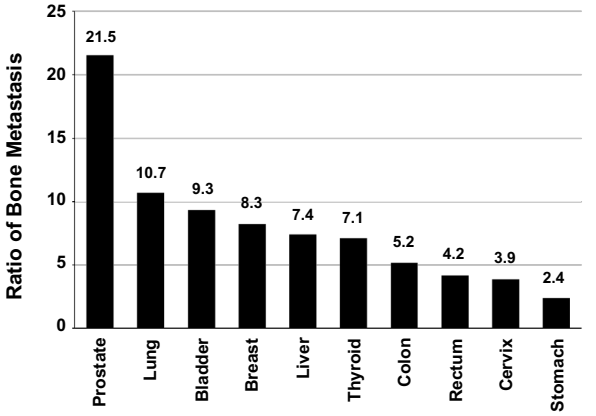

Figure 2. Ratio of Bone Metastasis with Each Type Of Primary Cancer

Survival rate of cancer patients with bone metastasis

The average median survival time of all types of bone metastases was 6 months, and the overall survival rates at 3, 6, 9, 12, and 24 months were 66.3%, 49.9%, 39.1%, 30.6% and 16.0%, respectively. Median survival times and survival rates for each type of primary cancer after bone metastasis are shown in Table 2. Stomach and lung cancers are considered to have a very fast disease progression after bone metastasis, presenting a median survival time less than three months. Another short survival group was liver cancer with a median survival time of between 3 and 6 months (Figure 3A). One of the intermediate survival time groups was urinary bladder cancer with a median survival time of between 6 and 9 months. Long survival groups included cancer of the cervix and breast with a median survival time of between 9 and 12 months (Figure 3B).

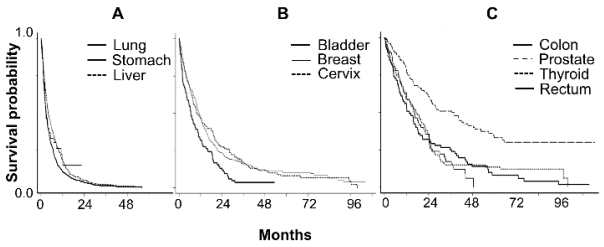

Figure 3. Kaplan Meier Curves of Survival Patterns. Median survival times of less than 6 months (A), 6 to 12 months (B), and more than one year (C)

The very long survival groups were those with cancer of the rectum, colon, thyroid and prostate which had a median survival time of more than one year. Kaplan Meier curves of patterns of survival of these cases are presented in Figure 3C.

Skeletal-related events (data from 2011-2015, OLARN Center)

This study reviewed 1,415 cases of bone metastasis including type of SREs and interventions, 48.9% of which required surgical intervention or radiation to improve performance status. Non-specific bone metastases without clinical symptoms and therapeutic interventions for bone metastasis were the most common (51.1%). The types of primary cancers which presented SREs are shown in Table 3.

Discussion

The number of bone metastasis patients in different countries varies and is shaped by the incidence of primary cancers and by the osteophilic properties of each type of cancer. A study of 2,641 bone metastases in Japan found the origins of the three most common carcinoma metastases were from lung, prostate and liver cancer (Takagi et al., 2015). The three leading bone metastases in the US originated from breast, prostate and lung cancer (Li et al., 2012; Oster et al., 2013). In Germany, the top three originated from breast, lung and prostate cancer (Tarnoki et al., 2016), in the UK the top three bone metastases originated from breast, prostate and thyroid cancer (Coleman, 2001), and in Malaysia the top three originated from breast, lung and prostate cancer (Singh et al., 2014). The prevalence of bone metastasis in Thailand is similarly closely related to the incidence of primary cancer in country. The greatest number of bone metastasis originated from lung cancer as lung cancer is the most common cancer among the Thai population and because it has strong osteophilic properties. As with lung cancer, there is a high prevalence of liver cancer in Thailand. Liver cancer also presented a strikingly high number of bone metastases, although it did not show as high an osteophilic ratio as prostate or lung cancer. These findings are similar to those reported from Khon Kaen University, Thailand. That retrospective study of 82 patients with spinal metastases found that the two leading bone metastases originated from cancer of the lung and liver (cholangiocarcinoma) (Paholpak et al., 2012).

Identification of primary cancer in patients suspected bone metastasis in adults and elderly patients is a critical step. Decision-making regarding metastasis is even more difficult in urgent situations including spinal cord compression and pathological fracture. At the same time, primary tumor identification is time-consuming and involves multiple investigative steps (Takagi et al., 2015). Knowledge of the relative prevalence of common bone metastases would facilitate establishing a strategy for selecting optimum investigation procedures which would reduce the time and cost of treatment while increasing overall effectiveness. Based on our findings, prevalence of bone metastasis begins to increase in patients at about age 46 (mean-1SD). Overall, the three most common origins of bone metastasis are cancer of the lung, liver, and breast which together account for 68.8% of all bone metastases. Therefore, effective and simple investigations of primary cancer in Thai people suspected of having bone metastases would focus on chest x-rays, liver palpation and ultrasound plus digital breast examination for women (to rule out breast cancer). Those methods are effective in nearly 70% of cases of bone metastasis.

Clinical presentation of bone metastasis in Thailand includes a high number of SREs without a preexisting history of primary cancers; however, surgical intervention for urgent conditions usually have to be delayed until the primary cancer has been identified. Forty-four percent of all bone metastasis cases included in this study originated from lung and liver cancers. Lung cancer is known to have a fast progression and short latency time (Nguyen et al., 2009), which was relating to skeletal-related events presentation before or concurrent primary tumor was diagnosed. Bone metastasis concurrent with lung cancer diagnosis has been reported in between 38.4% and 41.0% of cases (Tsuya et al., 2007). Those numbers are likely an underestimation as the sensitive investigation of bone metastasis is recommended when clinical suggestions (D'Addario et al., 2010). Cholangiocarcinoma has been reported as the major type of liver cancer in Thailand (Thunyaharn et al., 2013; Khuntikeo et al., 2015). Non-hepatocellular carcinoma, particularly cholangiocarcinoma, occasionally present skeletal events concurrent with or before primary cancer has been diagnosed (Goodwin et al., 2016). Bone metastasis in hepatocellular carcinoma presents in 16 to 25.4% of cases (Uchino et al., 2011; Abbas et al., 2014). The median time for the appearance of symptoms of bone metastasis after diagnosis of hepatocellular carcinoma is around 20 days (Kim et al., 2008).

Bone metastases from lung and liver cancer present a very short survival period (less than 6 months). Surgical intervention for palliative care should be optimized based on post-operative outcome, expected survival period, and general performance status. Available predictive scores, including the Tokuhashi score, have a low predictive ability for estimating survival periods of less than one year (Zoccali et al., 2016). Meanwhile, there are limited effective predictive scores which are able to help select cases with a good prognosis. Good prognostic factors in bone metastasis from lung cancer depend on good performance status (ECOG 0-1), single bone metastasis presentation and receipt of EGFR TKI treatment (Bae et al., 2012). For liver cancer, the presentation of ascites at the initial diagnosis of bone metastasis was the only factor indicating a poor prognosis (Kim et al., 2008). There have been few reports describing poor prognostic factors in bone metastasis patients and in patterns of cholangiocarcinoma (Habermehl et al., 2011; Katayose et al., 2012).

Patients with bone metastasis from breast cancer are considered to be in the intermediate survival group. A previous study of breast cancer of bone metastasis showed that the probability of bone metastasis occurred 13.2% from stage I, II and III (Liede et al., 2016), and about 5 to 6% of females presented with distant metastasis at initial diagnosis with bone as the most common site (Ibrahim et al., 2013). Breast cancer is easily detected by a physical examination and it is a relatively slow progressing cancer compared to lung and liver cancer. Bone metastasis from breast cancer is usually found during follow-up rather than

concurrent with initial diagnosis, so the clinical challenge for bone metastasis in breast cancer is early detection before the emergence of SREs during treatment.

Bone metastasis is less common in cervical cancer, with rates of 1.1 to 3.8% (Thanapprapasr et al., 2010). However, due to the high prevalence of cervical cancer in the Thai population, there are a high number of bone metastases from cervical cancer. Most bone metastases are found subsequent to initial diagnosis (Thanapprapasr et al., 2010; Makino et al., 2016), so late detection and under treatment of bone metastasis might be a special concern in the case of cervical cancer. Prostate cancer is not a leading cancer in the Thai population, but the osteophilic property of this cancer increases the number of bone metastases from prostate, making it the fifth most common form. Bone metastasis in prostate presented is very often asymptomatic. Osteoblastic metastases are more mechanically stable than that osteolytic metastasis of other types of primary cancer.

In conclusions, Bone metastasis is a single condition which has a wide range of clinical presentations and different prognoses. Skeletal-related events management depends on the type of primary cancer and the expected survival period. Early detection and rapid diagnosis can facilitate effective management for maintaining the maximum possible quality of life. This study presents fundamental data on the prevalence of bone metastasis patients at Chiang Mai University Hospital which serves the major part of the northern region of Thailand. Results from this study can help in the development of guidelines for primary cancer identification in general practice. Bone metastases from lung, liver, breast, cervix and prostate cancer are common in clinical practice. Further studies of the clinical course after bone metastasis of the top five cancers leading to bone metastasis should be conducted in order to establish criteria for optimal management during palliative care.

Acknowledgements

This research received funding from the Faculty of Medicine, Chiang Mai University. Additional support was provided by the Excellence Center in Osteology Research and Training Center (ORTC), Chiang Mai University, and The Thailand National Research University (NRU) Fund. The authors would also like to express their sincere thanks to Dr. G. Lamar Robert for editing the English manuscript.

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