Incidence and Prognosis of Bone Metastases in Common Solid Cancers at Initial Diagnosis: A Population-Based Study

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Abstract

Background Bone is one of the most common sites of advanced tumors. However, there is currently a lack of population-based surveys for the incidence and prognosis of bone metastases in common solid cancers.

Methods Patients with 12 types of primary cancer and bone metastases at initial diagnosis between 2010 and 2015 were identified using the Surveillance, Epidemiology, and End Results (SEER) database. The Kaplan-Meier method and Cox logistic regression were conducted to analyze survival and the effect of bone metastases on different cancers.

Results We included 89,782 patients with bone metastases at cancer diagnosis. Lung cancer had the highest incidence (17.61%) of bone metastases at diagnosis in any stage, followed by liver cancer (6.29%), nasopharyngeal carcinoma (6.22%) and renal cancer (5.19%). Among patients with breast and prostate cancer, only 3.4% and 4.39%, respectively, were identified as having bone metastases at diagnosis. Breast cancer (32.1%), prostate cancer (25.2%), thyroid cancer (46.8%) and nasopharyngeal carcinoma (24.8%) patients with only bone metastasis have an over 20% five-year survival rate. Compared with patients at a stage previous to metastasis, bone metastasis significantly increased the risk of mortality and reduced survival time, especially for patients with prostate cancer (HR: 19.64, 95% CI 18.36 to 21.02). Concomitant other organ metastases make patient survival worse. Regarding the metastases of prostate cancer, bone metastases are the main type, while for colorectal cancer, bone metastases and concomitant visceral metastases mainly occur.

Conclusions The findings of this study provide estimates of the incidence and prognosis of patients with bone metastases during the initial diagnosis of common solid cancers. In addition, we also clarified the degree to which bone metastasis affects patient survival. Patient prognosis depends on the primary type of cancer. These results can be used as a reference for the screening of metastases, and the optimization of personalized treatment options to improve the quality of life and survival of patients.

Introduction

Bone is one of the most common sites of advanced cancer metastasis, especially in lung cancer, breast cancer and prostate cancer [1, 2]. With the development of medical technology, the survival of patients with different cancers has improved significantly, but the number of patients with bone metastases appears to be increasing in the past decades [3, 4]. The tumor causes a loss of bone mass in several different ways leading to skeletal related events (SREs) defined as pathological fractures, severe bone pain, the need for radiotherapy, spinal cord compression, and hypercalcemia [5–7]. Bone pain is the most common symptom [8]. Patients with bone metastases develop their first SRE shortly after diagnosis and most of them suffer from at least one SRE which results in increased cost and poor prognosis and quality of life [9–13].

The earlier bone metastases are diagnosed and treated, the greater the benefit to the patient. The treatment of bone metastases aims to relieve symptoms, preserve or reconstruct function and improve the quality of life, but it requires a deep understanding of the underlying diseases [5, 14, 15]. In most literature, data on bone metastases are based on a single tumor. Previous studies have reported that the prognoses of patients with breast, prostate and thyroid cancer with bone metastases are significantly superior to those of patients with lung and gastrointestinal cancer [16–18]. The survival of patients with bone metastases is related to the characteristics of their primary tumors.

A better understanding of the survival of these cancers with bone metastases can aid preliminary treatment strategies including radiotherapy, operation, targeted therapy and so on, especially for patients who need surgery for severe bone structure destruction or pathologic fracture [8, 19–21]. The benefit of the patient is the first consideration when choosing

a treatment. However, large-scale studies on the incidence and prognosis of bone metastases in common solid tumors are still rare.

In this study, the objective was to use the Surveillance, Epidemiology, and End Results (SEER) database to survey the incidence and prognosis of patients with bone metastases during diagnosis in 12 common solid malignant tumors [4]. We also attempted to compare the prognosis of three stages of tumors, namely, stage previous to metastasis, bone metastases only and bone metastases with other synchronous metastases to investigate the impact of bone metastasis on patients.

Materials And Methods

We used data from the SEER database sponsored by the National Cancer Institute. This database collects and publishes cancer incidence, treatment and survival data, which consists of 18 population-based registries of SEER data, covering approximately 28% of the United States population. We identified eligible patients using the SEER*Stat version 8.3.5 software (http://www.seer.cancer.gov/seerstat).

Information on the presence or absence of metastases at the time of diagnosis has been made available since 2010. We included patients diagnosed with microscopically confirmed primary malignancy between 2010 and 2015 that originated in the following sites: lung and bronchus, breast, prostate, liver, kidney, bladder, stomach, colon, rectum, thyroid, nasopharynx and cervix uteri. Patients were excluded if the state relating to the presence or absence of metastases was unknown or not available. In total, 1,401,451 patients were eligible including 79,782 diagnosed with bone metastases in the cohort analyzed for incidence. We excluded patients with incomplete follow-up data and a survival month of zero, leaving 141,967 patients eligible for survival analyses.

Statistical analysis

We examined common primary cancer types with bone metastases. Patients were stratified by cancer type. Absolute numbers and incidence proportions were computed for patients with bone metastases at the time of their primary cancer diagnosis. The incidence proportion was defined as the percent of primary cancer patients with bone metastases among the total study cohort or among the patients with metastatic disease to any other site.

We stratified the stage previous to metastases, bone metastases only and bone plus other sites of metastases, including the lungs, brain and liver at the time of diagnosis according to the American Joint Committee on Cancer (AJCC) staging system (2010, 7th vision) in SEER software. Patients with follicular thyroid carcinoma or papillary thyroid carcinoma under 45 years of age with metastases were stage II. We calculated the 1-year, 3-year, 5-year and median survival times using the Kaplan-Meier method. We conducted Cox logistic regression to compute the hazard ratios (HRs) for death and the corresponding 95% confidence intervals (Cis) separately for each cancer above, comparing the stage previous of metastasis, bone metastases only and bone metastases plus other synchronous metastases.

We used SPSS statistical software version 21.0 (Chicago, USA) for all statistical analyses and $P < 0.05$ was considered statistically significant.

Results

There are significant differences in the number and proportion of patients with bone metastases at diagnosis depending on the primary tumor type (Table 1). A total of 1,401,451 patients were newly diagnosed with a solid malignancy and 79,782 had bone metastases according to SEER database between 2010 and 2015. Out of all of the 1,401,451 study patients, lung, breast and prostate cancer were the most common primary tumor types of bone metastases. Lung cancer

had the highest incidence proportion (17.61%) of bone metastases at diagnosis in any stage, followed by liver (6.29%), nasopharynx (6.22%) and renal cancer (5.19%) whose incidence proportion was over 5%. Among patients with breast and prostate cancer, only 3.4% and 4.39%, respectively, were found to have bone metastases at diagnosis. The incidence proportion of bone metastases was higher in patients with any distant metastases in each type of tumor which from high to low were breast cancer (64.98%), prostate cancer (59.98%), nasopharyngeal carcinoma (53.69%), lung cancer (36.20%), renal cancer (35.02%), liver cancer (34.43%) and thyroid cancer (31.60%).

Table 1
The number and incidence proportion of patients diagnosed with bone metastases.

Primary sites of cancer	Total number patients with cancer	Total number patients with distant metastases at diagnosis	Number of patients with bone metastases at diagnosis	Incidence proportion of bone metastases in all patients (%)	Incidence proportion of bone metastases in patients with distant metastases(%)
Lung and Bronchus	249295	121270	43905	17.61	36.20
Breast	358896	19158	12448	3.47	64.98
Prostate	283699	20747	12444	4.39	59.98
Liver	18164	3320	1143	6.29	34.43
Renal	75580	11205	3924	5.19	35.02
Bladder	102859	7201	1338	1.30	18.58
Stomach	32306	11722	1470	4.55	12.54
Colon	141752	28436	1392	0.98	4.90
Rectum	43571	7283	599	1.37	8.22
Thyroid	73855	1595	504	0.68	31.60
Nasopharynx	3040	352	189	6.22	53.69
Cervix uteri	18434	2500	426	2.31	17.04

The survival of patients in three different conditions (stage previous to metastases, bone metastases only and bone combined with other sites of metastases) at diagnosis varied depending on the primary cancer type (Table 2). One-year survival ranged from 82.0% for bone metastases only secondary to breast cancer to 15.7% for stomach cancer. Three-year survival was highest in patients with thyroid cancer (64.2–74.9%) and lowest in those with stomach cancer (2.5%). Breast cancer (32.1%), prostate cancer (25.2%), thyroid cancer (46.8%) and nasopharyngeal carcinoma (24.8%) patients with only bone metastases have an over 20% five-year survival rate. Liver cancer patients with bone metastases experienced the shortest median survival (4 months). The survival curves of the three states are presented in Fig. 1. We also used a univariate Cox proportional hazards model to analyze the influence of metastases on survival (Table 2). Compared with patients at a stage previous to metastases, bone metastasis significantly increased the risk of mortality and reduced survival time especially for patients with prostate cancer (HR: 19.64, 95% CI 18.36 to 21.02). Interestingly, patients with thyroid cancer and bone metastases had a longer survival than those with stage IVB cancer without any distant metastases (median survival 60 months vs 32 months). In prostate cancer, the number of patients with simple bone metastases is much greater than those with concomitant other site metastases. Conversely, in patients with colorectal cancer, multiple organ metastases are dominant. When other concomitant organ metastases exist, the survival

of patients becomes worse and the risk of death is further aggravated, but in gastric cancer and liver cancer, this factor has a smaller effect on patient survival time.

Table 1

The survival and HRs for mortality after bone metastases, comparing patients with stage previous to metastasis, bone metastases only and bone metastases with other synchronous metastases.

Primary sites of cancer		Number	1-year survival %	3-year survival %	5-year survival %	Median survival (month, 95%CI)	Log-rank P-value	HR (95%CI)
Lung and Bronchus	The stage previous to metastases (IIIB)	14368	50.8	19.8	12.9	13(12.68–13.32)	< 0.001	1.00
	Bone metastases only	16117	27.6	7.0	3.5	6(5.84–6.16)		1.78(1.75–1.84)
	Bone + other sites metastases	20995	20.1	3.7	1.4	5(4.89–5.12)		2.23(2.17–2.28)
Breast	The stage previous to metastases (IIIC)	8706	93.5	74.5	61.0	NA	< 0.001	1.00
	Bone metastases only	6777	82.0	51.8	32.1	38(36.67–39.33)		2.33(2.20–2.46)
	Bone + other sites metastases	4619	64.2	32.6	16.3	21(19.86–22.14)		4.23(3.99–4.48)
Prostate	The stage previous to metastases (III)	24896	99.0	96.2	92.3	NA	< 0.001	1.00
	Bone metastases only	11593	77.2	41.7	25.2	29(28.11–29.89)		19.64(18.36–21.02)
	Bone + other sites metastases	1166	58.1	27.7	18.5	16(14.07–17.93)		32.37(29.36–35.69)
Liver	The stage previous to metastases (IVA)	648	30.2	10.1	6.4	6(5.27–6.73)	< 0.001	1.00
	Bone metastases only	661	19.1	2.6	1.0	4(3.52–4.48)		1.34(1.19–1.51)
	Bone + other sites metastases	251	12.5	1.2	NR	3(2.58–3.42)		1.76(1.51–2.06)
Renal	The stage previous to metastases (III)	11385	89.6	73.7	63.3	NA	< 0.001	1.00

Primary sites of cancer		Number	1-year survival %	3-year survival %	5-year survival %	Median survival (month, 95%CI)	Log-rank P-value	HR (95%CI)
	Bone metastases only	1561	50.7	24.3	14.1	13(11.85–14.15)		5.00(4.65–5.37)
	Bone + other sites metastases	1955	28.2	7.7	3.8	6(5.57–6.43)		9.40(8.81–10.04)
Bladder	The stage previous to metastases (III)	3886	66.8	40.5	31.4	24(22.26–25.74)	< 0.001	1.00
	Bone metastases only	702	26.0	5.4	1.1	6(5.25–6.78)		3.40(3.10–3.74)
	Bone + other sites metastases	446	14.0	1.8	NR	4(3.32–4.68)		4.88(4.37–5.45)
Stomach	The stage previous to metastases (IIIC)	1621	56.8	20.0	12.2	14(13.16–14.84)	< 0.001	1.00
	Bone metastases only	631	15.7	2.5	1.8	5(4.39–5.62)		2.81(2.53–3.12)
	Bone + other sites metastases	553	18.7	4.2	2.1	5(4.43–5.57)		2.69(2.41–3.01)
Colon	The stage previous to metastases (IIIC)	7884	77.3	50.5	38.2	37(35.06–38.94)	< 0.001	1.00
	Bone metastases only	80	39.0	20.3	NR	7(2.57–11.43)		3.02(2.31–3.94)
	Bone + other sites metastases	958	29.9	4.3	2.0	5(5.17–6.83)		4.55(4.20–4.92)
Rectum	The stage previous to metastases (IIIC)	1711	85.1	57.1	42.2	45(39.99–50.01)	< 0.001	1.00
	Bone metastases only	61	59.8	16.0	NR	17(12.78–21.22)		3.03(2.19–4.20)
	Bone + other sites metastases	386	41.7	10.9	NR	10(8.37–11.63)		4.71(4.08–5.45)

Primary sites of cancer		Number	1-year survival %	3-year survival %	5-year survival %	Median survival (month, 95%CI)	Log-rank P-value	HR (95%CI)
Thyroid	The stage previous to metastasis(IVB)	640	61.0	48.3	41.3	32(19.44–44.56)	< 0.001	1.00
	Stage II with bone metastasis	26	74.9	74.9	NR	52(0-109.63)		0.62(0.31–1.25)
	Bone metastases only	220	78.5	64.2	46.8	60(51.09–68.91)		0.65(0.50–0.84)
	Bone + other sites metastases	211	44.8	24.2	16.2	10(6.83–13.17)		1.80(1.47–2.21)
Nasopharynx	The stage previous to metastasis(IVB)	351	84.0	62.7	49.2	57(NA-NA)	< 0.001	1.00
	Bone metastases only	75	65.8	29.7	24.8	17(10.08–23.92)		2.40(1.66–3.45)
	Bone + other sites metastases	97	56.2	11.6	NR	15(10.68–19.32)		3.49(2.55–4.77)
Cervix uteri	The stage previous to metastasis(IVA)	350	59.7	30.1	26.1	16(13.26–18.75)	< 0.001	1.00
	Bone metastases only	184	47.2	16.6	12.1	12(9.48–14.52)		1.47(1.18–1.85)
	Bone + other sites metastases	196	24.6	7.3	4.6	6(4.90–7.10)		2.55(2.06–3.16)

Abbreviations: NR=not reached, NA=not applicable

Discussion

Bone metastases frequently happen in solid tumors, and are related to SREs which are associated with poor prognosis and an impaired quality of life. To help patients make appropriate decisions about their treatment alternatives, it is essential to understand the incidence and prognosis of bone metastases even when combined with visceral metastasis. In this study, we analyzed the recent data from the SEER database on the incidence proportion and prognosis of patients with bone metastases secondary to 12 specific common solid tumors at the initial diagnosis. At the same time, we compared the risk of mortality and the survival time in three stages of tumors to explore the effect of bone metastasis on tumors. The data in this study could be applied broadly and influence screening paradigms for bone metastases to guide treatment, design clinical trials and counsel specific subsets of patients with cancer.

This study has several limitations. First, bone metastases in our study were identified at initial cancer diagnosis. The SEER database does not provide information on the progress of cancer, so we were unable to identify patients who

developed bone metastases following the initial diagnosis. Second, routine screening for bone metastases is recommended in case there are signs or symptoms in some tumors. Therefore, some early stage asymptomatic patients were missed diagnoses resulting in an underestimation of the actual incidence of bone metastases. Third, we do not know the location, size and number of bone metastases. Additional bone metastases would increase more the risk of mortality compared with single bone metastasis which may influence the survival estimate. Similarly, we also offer data about the proportion of SREs in patients with bone metastases. Some studies have demonstrated that SREs are one of the predominant factors in unfavorable prognoses.

Although there are the abovementioned limitations, our results provide a large-scale epidemiological analysis of bone metastases because the SEER program encompasses 28% of the United States. The skeletal system is one of the most frequently mentioned metastatic sites in advanced cancer. Bisphosphonates are recommended for the prevention of SREs. However, some research has found that only a few patients with bone metastases undergo treatment of bisphosphonates [22, 23]. Early screening, prevention and treatment are important in the process of management. With the use of PET and CT, Michael et al found a higher incidence of bone metastases in lung cancer patients, ranging between 20–40% compared to 7–20% before the 20th century and 40–80% of these cases were detected at the time of the initial period. In addition, multiple bone metastases are present in approximately 80% of cases, far more than single bone metastases [24, 25]. The most frequent site of bone metastasis was the spine, followed by the pelvis and long bones [26]. Our findings are consistent with those of previous studies showing that bone metastases from the lung, breast and prostate are the most common and account for 68% of all metastatic bone diseases [1, 2]. Prostate cancer has the highest 5-year cumulative incidence of bone metastases (24.5%), followed by lung (12.4%) renal (8.4%) and breast cancer (6.0%) whose 5-year cumulative incidence is higher than 5% in their research. A population study in Denmark showed that the incidence of bone metastases in prostate cancer was only 3% at initial prostate cancer diagnosis based on the Danish National Patient Registry [27]; similarly, this figure is 4.39% at the initial diagnosis in our study. For bone metastases, different primary tumors have different risk factors. The incidence of bone metastases in lung cancer reported by Gustavo et al and Katrin et al depended on the histological subtype [22, 23]. For breast cancer, it has been demonstrated that patient age, hormone receptor status, human epidermal growth factor receptor 2 and tumor size contribute to bone metastases [28, 29]. Ruatta et al reviewed and analyzed renal cancer patients in their clinics and found that approximately 4% of patients had bone metastases at the time of initial diagnosis, while approximately 13% of patients had metastases during follow-up [30]. Compared with other primary tumors in urinary cancer, bladder cancer has a lower incidence of bone metastases in our research. Several studies have documented that the incidence of bone metastases in gastrointestinal tumors ranges from 3–7% in the course of disease [17, 31]. In most retrospective reports, only the incidence of bone metastases was considered and the period in which it occurred was not indicated. Therefore, this may be one of the reasons for the difference in incidence in some studies. In addition, the proportion of patients with bone metastases may be underestimated in the public registered database because of the proportion of asymptomatic metastatic patients. Overall, our study results are consistent with the epidemiology of bone metastases in common solid tumors and patient survival depends on the type of primary tumor.

Metastasis is one of the main reasons leading to mortality, especially the metastasis of vital organs. A study in Norway revealed that for all solid tumors, 66.7% of cancer deaths are caused by metastases [32]. Bone, as a supporting structure, plays a critical role in movement and is also the main site of hematopoiesis. How much damage regarding survival and prognosis can bone metastases cause to patients? Bone metastases tend to reduce survival, which depends on the type of primary tumor and the presence of other visceral metastases. Patients with bone metastatic breast and prostate cancer have relatively better survival than those with lung cancer [24, 33, 34]. Patients with bone metastases exhibited better survival than those with other single site metastases, and synchronous other site metastases further impaired the survival in patient with breast and prostate cancer. Conversely, in other tumors, such as lung cancer and colorectal cancer, patients have poor survival [35, 36]. Bone metastasis as the only metastatic site reduces the 2-year overall survival from 35.5–15.8% in urothelial carcinoma [37]. In the research, the authors think that patients with bone metastases are less likely to

receive systematic therapy than other metastases because of the lower Performance Status (PS) score which may be one of the reasons for their worse survival. In our study, patients with bone metastases secondary to thyroid carcinoma had the longest survival time, especially young patients. Through comprehensive treatment, their 5-year survival rate reached 69%, which was significantly higher than that of patients treated with I131 alone [38]. We found that patients with thyroid cancer with only bone metastases had a better prognosis than patients with local progression whose tumor invaded the prevertebral fascia or encased the carotid artery or mediastinal vessels(T4b). Like other tumors, the prognosis of these patients becomes worse when there are other sites of metastases. We also presented the number of patients with only bone metastases and contemporaneous extraosseous metastases in different tumors to offer some effective clues for the metastasis screening of cancer patients. Patients often suffer from a tumor with multiple metastases and clinicians need to be alert as to whether there are other metastases in patients with bone metastases.

Conclusion

Our study presents the incidence and survival of patients with bone metastases at the initial diagnosis of common solid cancers based on a population-based analysis from SEER data. At the same time, we also clarified the effect of bone metastases on the survival time of patients which depends on the primary type of cancer. Using these results, we can better assess the patient's survival status and choose the appropriate treatment to obtain the most benefit. In addition, we can use these data as a reference to guide the screening of bone metastases for early diagnosis and treatment, and to reduce the occurrence of bone-related events.

Abbreviations

SEER
The Surveillance, Epidemiology, and End Results; OR:Adjusted odds ratio; CI:Confidence interval; HR:hazard ratio; SREs:skeletal related events.

Declarations

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Authors' contributions

Study design: JZ. Acquisition of data: JZ, QW and SH. Analysis and interpretation of data: JZ, DC and JP. Writing, review, and/ or revision of manuscript: JZ, QW. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Cancer a reportable disease in every state in the United States; informed patient consent is not required for the data released by the SEER database.

Consent for publication

Not applicable

Competing interests

The authors declare they have no competing interests.

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Figures

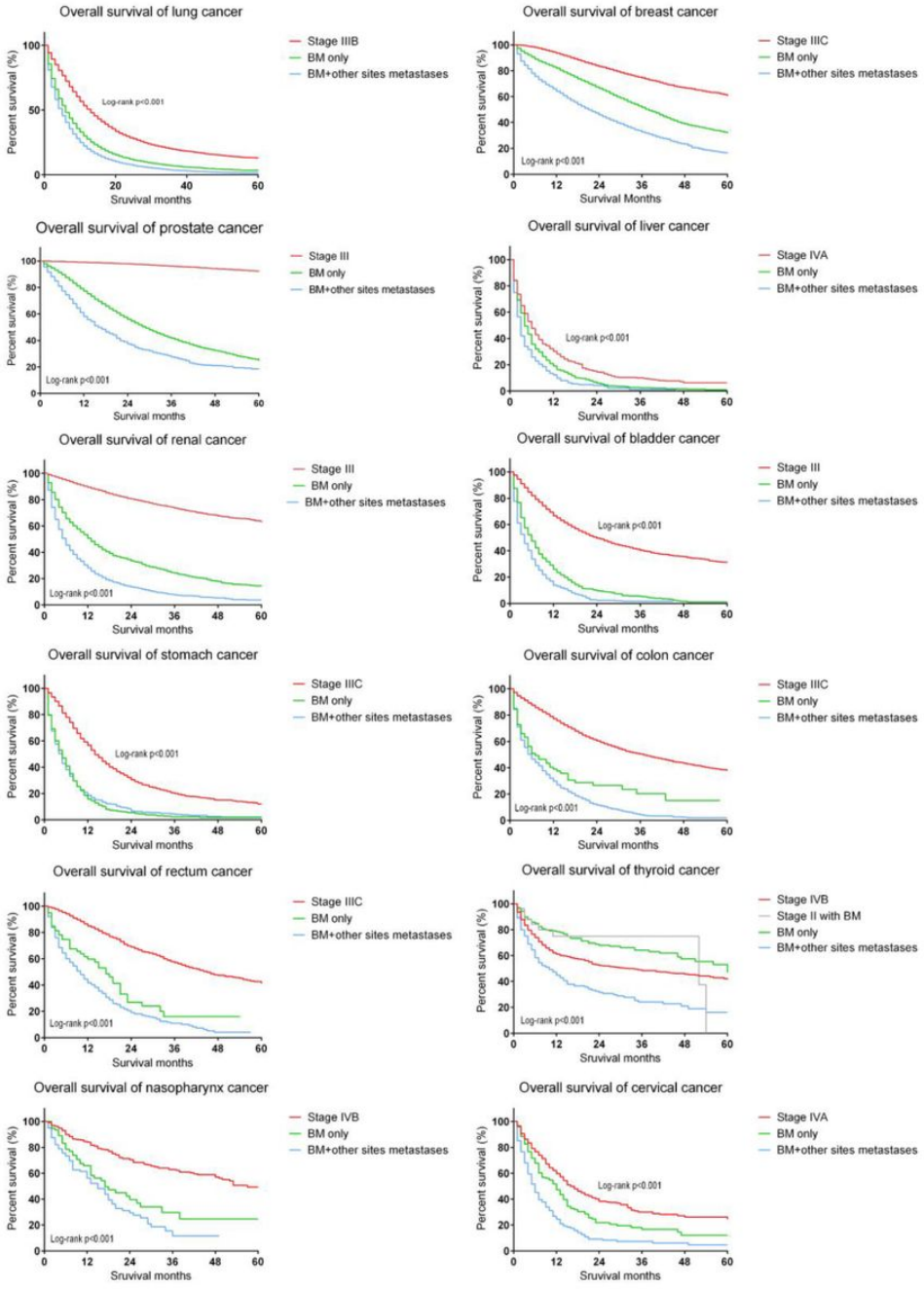

Figure 1

Cumulative survival of patients with stage previous to metastasis, bone metastases only and bone metastases with other synchronous metastases.