Original Article

Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study

Jin-Feng Huang[1], Jianfei Shen[2], Xiao Li[3], Ramesh Rengan[4], Nicola Silvestris[5,6], Minqi Wang[7], Lisa Derosa[8], Xuanqi Zheng[1], Andrea Belli[9], Xiao-Lei Zhang[1], Yan Michael Li[10], Aimin Wu[1]

[1]Department of Orthopaedics, Zhejiang Provincial Key Laboratory of Orthopaedics, The Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China; [2]Department of Cardiothoracic Surgery, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai 317000, China; [3]Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Affiliated Cancer Hospital of Nanjing Medical University, Nanjing 210009, China; [4]Department of Radiation Oncology, University of Washington School of Medicine, Washington, USA; [5]IRCCS Istituto Tumori "Giovanni Paolo II" of Bari, Bari, Italy; [6]Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy; [7]Department of Orthopaedics, Shanghai Key Laboratory of Orthopaedic Implants, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China; [8]U1015, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, Villejuif, France; [9]Department of Abdominal Oncology, National Cancer Institute-Fondazione "G Pascale", IRCCS, Naples, Italy; [10]Department of Neurosurgery and Oncology, University of Rochester Medical Center, School of Medicine and Dentistry, Rochester, NY, USA

Contributions: (I) Conception and design: JF Huang, YM Li, A Wu; (II) Administrative support: YM Li, A Wu; (III) Provision of study materials or patients: JF Huang, J Shen, X Li; (IV) Collection and assembly of data: JF Huang, J Shen, X Zheng; (V) Data analysis and interpretation: JF Huang, J Shen, X Li, X Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Aimin Wu, MD, PhD. Department of Spine Surgery, Zhejiang Spine Surgery Centre, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, 109# Xueyuan Road, Wenzhou 325027, China. Email: aiminwu@wmu.edu.cn; Yan Michael Li, MD, PhD. Department of Neurosurgery and Oncology, University of Rochester Medical Center, School of Medicine and Dentistry, URMC 601 Elmwood Ave, Rm 2.8121, Box 670 Rochester, NY 14642, USA. Email: yanm_li@urmc.rochester.edu.

Background: Bones are one of the most common metastatic sites for solid malignancies. Bone metastases can significantly increase mortality and decrease the quality of life of cancer patients. In the United States, around 350,000 people die each year from bone metastases. This study aimed to analyze and update the incidence and prognosis of bone metastases with solid tumors at the time of cancer diagnosis and its incidence rate for each solid cancer.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) database to find patients diagnosed with solid cancers originating from outside the bones and joints between 2010 and 2016. Data were stratified by age, sex, and race. Patients with a tumor *in situ* or with an unknown bone metastases stage were excluded. We then selected most of the sites where cancer often occurred, leaving 2,207,796 patients for the final incidence analysis. For the survival analysis, patients were excluded if they were diagnosed at their autopsy or on their death certificate, or had unknown follow-ups. The incidence of bone metastases and overall survival was compared between patients with different primary tumor sites.

Results: We identified 2,470,634 patients, including 426,594 patients with metastatic disease and 113,317 patients with bone metastases, for incidence analysis. The incidence of bone metastases among the metastatic subset was 88.74% in prostate cancer, 53.71% in breast cancer, and 38.65% in renal cancer. In descending order of incidence, there were patients with other cancers in the genitourinary system (except for renal, bladder, prostate, and testicular cancer) (37.91%), adenocarcinoma of the lung (ADC) (36.86%), other gynecologic cancers (36.02%), small-cell lung cancer (SCLC) (34.56%), non-small cell lung cancer not otherwise specified and others [NSCLC (NOS/others)] (33.55%), and bladder (31.08%) cancers. The rate of bone metastases is 23.19% in SCLC, 22.50% in NSCLC (NOS/others), 20.28% in ADC, 8.44% in squamous cell carcinoma of the lung (SCC), and 4.11% in bronchioloalveolar carcinoma [NSCLC (BAC)]. As for the digestive system, the overall bone metastases rate was 7.99% in the esophagus, 4.47% in the

gastric cancer, 4.42% in the hepatobiliary cancer, 3.80% in the pancreas, 3.26% in other digestive organs, 1.24% in the colorectum, and 1.00% in the anus. Overall, the incidence rate of bone metastases among the entire cohort in breast and prostate cancer was 3.73% and 5.69%, respectively.

Conclusions: The results of this study provide population-based estimates for the incidence rates of patients with bone metastases at initial diagnosis of their solid tumor. The findings can help clinicians to early detect bone metastases by bone screening to anticipate the occurrence of symptoms and favorably improve the prognosis.

Keywords: Bone metastases; Surveillance, Epidemiology, and End Results (SEER); incidence; prognosis

Submitted Dec 20, 2019. Accepted for publication Feb 25, 2020.
doi: 10.21037/atm.2020.03.55
View this article at: http://dx.doi.org/10.21037/atm.2020.03.55

Introduction

Bones are one of the most common sites of metastases for many types of solid cancers (1-4). Bone metastases have an increased risk of serious skeletal-related events (SREs), such as pathological fractures, pain, hypercalcemia, and spinal cord compressions, which can seriously impair patients' quality of life (5-9). Bone metastases also lead to a significant increase in mortality and morbidity (10-12).

In the United States, around 350,000 people die each year from bone metastasis (13). Several patients with bone metastasis and SREs are affected by breast or prostate cancer, while lower rates are observed in patients with lung, kidney, thyroid, or other cancers (4,14). The incidence rate of bone metastases in the United States is still unknown, and estimates have varied from 21,000–400,000 per annum. Though bone metastases can impact the mortality and quality of life of patients with cancer, more extensive population-based studies researching the incidence and prognosis of patients with bone metastases are lacking. Previous studies have shown that the prevalence of bone metastases is more than 70% in patients with metastatic breast and prostate cancer, and approximately 30% in metastatic renal cell carcinoma (1,12,15-18). However, there are no studies which provide information on the incidence of bone metastasis in other common cancers or systemic malignancies. Also, earlier studies cannot reflect the recent incidence and survival trends of patients with bone metastases (19).

Our study was conducted to estimate the incidence and prognosis of patients with bone metastases using the Surveillance, Epidemiology, and End Results (SEER) database that includes information on cancer incidence, treatment, and survival for approximately 30% of the American population (20). Specifically, we estimated the incidence proportion of patients' bone metastases among solid tumors, considering tumor histology at the time of initial diagnosis.

Methods

Data source and cohort population

For our study, the SEER database was used. Inclusion criteria were adult patients (age ≥18 years) with a diagnosis of an invasive solid tumor originating outside of the bone and joints between January 1, 2010, and December 31, 2016. Patients were excluded if information relating to the presence or absence of bone metastases was unavailable. Other exclusion criteria were patients with diagnosis of carcinoma *in situ* and patients with a diagnosis of a rare tumor such as thymus cancer, heart cancer, mediastinum cancer, pleura cancer, spleen cancer, reticuloendothelial cancer, skin cancer, connective and soft tissue cancer, adrenal gland cancer, parathyroid gland cancer, other endocrine gland cancer, mesothelioma, Kaposi sarcoma, and lymphoma. For the survival analysis, patients were excluded if they were diagnosed at the time of the autopsy or at the issuing of the death certificate, or if they had unknown survival time or survival status.

Statistical analysis

Total numbers and incidence proportions of patients who were diagnosed with bone metastases were computed and then stratified by cancer type. The patients with lung cancer were classified by tumor histology using the International Classification of Disease for Oncology,

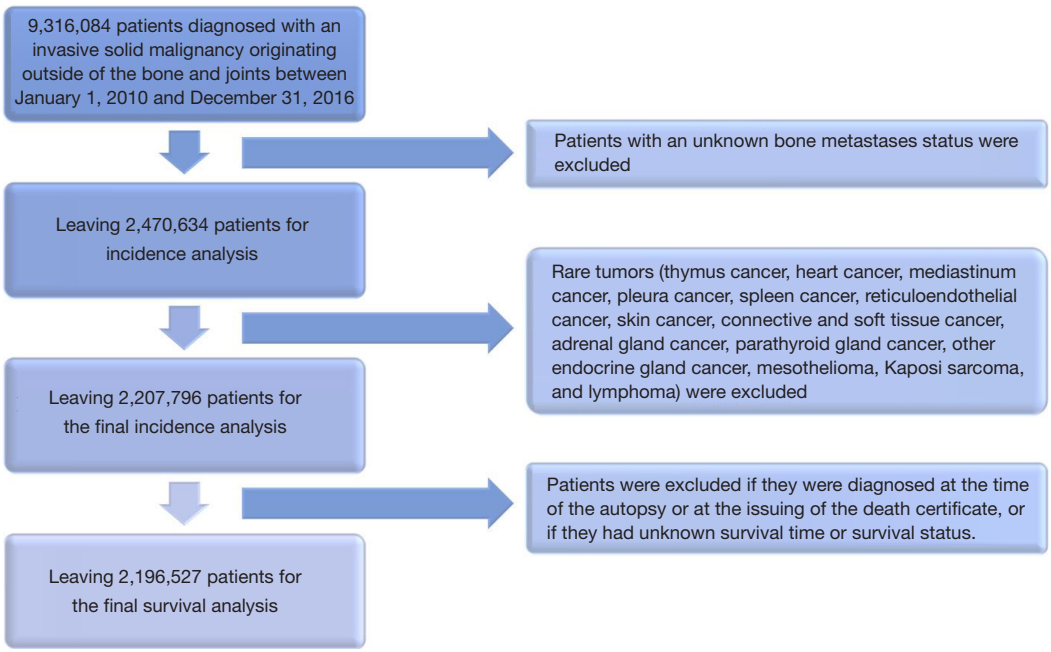

Figure 1 Selection of study patients.

3rd Edition (ICD-O-3). Metastatic stage was conducted following the 7th edition of the American Joint Committee on Cancer staging manual, and then we defined patients with metastatic cancer as a subset with metastatic disease. We defined patients with bone metastases as a subset with bone metastases. The incidence proportion was defined as the number of patients diagnosed with bone metastases and a specific primary cancer divided by the total number of individuals diagnosed with that primary cancer; we also defined a second incidence proportion in which the denominator was restricted to patients with metastatic disease. The metastatic status of the brain, lung, and liver was also available, and we used it to characterize the extent of systemic disease, and subsequently calculated the incidence and median survival of patients with bone metastases classified by the extent of systemic disease. For survival estimates, we used the Kaplan-Meier method, taking into account a P value ≤0.05 as significant. The statistical analysis was generated and visualized with SPSS software (version 18; IBM Corp., USA).

Results

First, we identified 9,316,084 patients aged ≥18 years who were diagnosed with an invasive solid malignancy originating outside of the bone and joints between January 1, 2010 and December 31, 2016. The SEER database includes information on cancer incidence, treatment, and survival for approximately 30% of the American population. Patients were excluded in the cohort if the carcinoma is was in situ. Patients with an unknown bone metastases stage were excluded, leaving 2,470,634 patients for analysis. We then selected most of the sites where cancer often occurred, leaving 2,207,796 patients for the final incidence analysis (*Figure 1*).

Between 2010–2016, a total of 2,207,796 patients had a diagnosis of cancer from common solid organs, and 426,594 patients had metastatic disease. We found 113,317 patients with bone metastases, which accounted for 5.13% of all patients, and 26.56% of those patients had metastatic disease.

Next, we found that the rate of bone metastases varied widely by primary cancer type (*Table 1*; *Figure 2*). As shown in *Table 1*, the bone metastasis rate is the highest in lung cancer. More specifically, the rate of bone metastases is 23.19% for small-cell lung cancer (SCLC), 22.50% in non-small cell lung cancer not otherwise specified and others [NSCLC (NOS/others)], 20.28% for adenocarcinoma of the lung (ADC), 8.44% in squamous cell carcinoma of the lung (SCC), and 4.11% in bronchioloalveolar carcinoma [NSCLC (BAC)]. In analyzing the gastrointestinal tumors, the rate of bone metastases is 7.99% in the esophagus,

Table 1 Incidence proportion and median survival of patients with identified bone metastases at diagnosis by primary cancer site

Site	Sub-site	Number of patients with cancer (any stage)	Number of patients with metastatic disease	Number of patients with bone metastases at diagnosis	Incidence proportion of bone metastases among entire cohort (%)	Incidence proportion of bone metastases among subset with metastatic disease (%)	Median survival in months (interquartile range) among patients with bone metastases (months)
Head and neck[1]	Head and neck[1]	77,610	11,267	1,114	1.44	9.89	8 [3–18]
Thyroid	Thyroid	88,356	3,347	679	0.77	20.29	23 [4–82]
Breast	Breast	436,347	30,285	16,266	3.73	53.71	27 [8–57]
Respiratory system	SCLC	39,765	26,686	9,223	23.19	34.56	5 [1–10]
	SCC	93,240	33,839	7,867	8.44	23.25	3 [1–7]
	ADC	147,194	80,981	29,846	20.28	36.86	5 [1–13]
	NSCLC (BAC)	4,475	1,024	184	4.11	17.97	7 [3–20]
	NSCLC (NOS/ others)	20,622	13,224	4,434	21.50	33.53	3 [1–8]
Digestive system	Esophagus	25,955	10,005	2,075	7.99	20.74	11 [4–36]
	Gastric	43,570	15,525	1,947	4.47	12.54	3 [1–8]
	Hepatobiliary	72,015	16,454	3,186	4.42	19.36	3 [1–7]
	Pancreatic	74,660	39,535	2,835	3.80	7.17	2 [1–6]
	Colorectal	249,273	52,311	3,085	1.24	5.90	5 [1–15]
	Anal	12,150	1,584	121	1.00	7.64	3 [NR–7]
	Other digestive organs	23,514	8,229	767	3.26	9.32	3 [1–8]
Genitourinary	Renal	101,121	14,498	5,630	16.08	38.65	6 [2–17]
	Bladder	124,279	5,921	1,840	1.48	31.08	4 [1–10]
	Prostate	346,844	22,257	19,750	5.69	88.74	25 [11–55]
	Testicular	16,661	1,993	143	0.86	7.18	NR [7–NR]
	Other GU	8,467	757	287	3.39	37.91	4 [1–9]

Table 1 (*continued*)

Table 1 *(continued)*

Site	Sub-site	Number of patients with cancer (any stage)	Number of patients with metastatic disease	Number of patients with bone metastases at diagnosis	Incidence proportion of bone metastases among entire cohort (%)	Incidence proportion of bone metastases among subset with metastatic disease (%)	Median survival in months (interquartile range) among patients with bone metastases (months)
Gynecologic	Ovarian	37,468	23,890	422	1.13	1.77	5 [1–17]
	Endometrial	93,149	8,304	847	0.91	10.20	6 [2–15]
	Cervical	22,774	3,585	558	2.45	15.56	6 [2–15]
	Other gynecologic	15,160	497	179	1.18	36.02	6 [2–16]
Brain and other nervous system	Brain and other nervous system	33,127	596	59	0.18	9.90	15 [3–NR]

[1], lip, tongue, gum, floor of mouth, & other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle & inner ear, larynx, trachea, orbit & lacrimal gland, retina, eyeball, eye, NOS. GI, gastrointestinal; GU, genitourinary; GYN, gynecologic; SCLC, small-cell lung cancer; NSCLC (NOS/others), non-small cell lung cancer not otherwise specified or non-small cell lung cancer other lung cancer; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung; NSCLC (BAC), bronchioloalveolar carcinoma; NR, not reached.

4.47% in the gastric system, 4.42% in the hepatobiliary system, 3.80% in the pancreas, 3.26% in other digestive organs, 1.24% in colorectum, and 1.00% in the anus. Among patients with renal cancer, prostate and breast cancer,16.08%, 5.69%, and 3.73% of patients were respectively found to have bone metastases.

Moreover, *Table 1* and *Figure 3* show the incidence proportion of patients with bone metastases among the metastatic subset (patients with stage IV disease at diagnosis). The incidence of bone metastases among the metastatic subset is 88.74% in prostate cancer, 53.71% in breast cancer, and 38.65% in renal cancer. In descending order, patients with other cancers of the genitourinary system (except renal, bladder, prostate, testicular) (37.91%), ADC (36.86%), other gynecologic cancers (except ovarian, endometrial, and endometrial cancer) (36.02%), SCLC (34.56%), NSCLC (NOS/others) (33.55%), and bladder cancer (31.08%), showed an incidence proportion of bone metastases of >30%.

Table 1 and *Figure 4* show the median survival time of patients with bone metastases in different systemic malignancies. The median survival time among patients with breast cancer and bone metastases, prostate cancer, and bone metastases and thyroid cancer, and bone metastases are 27, 25, and 23 months, respectively. The survival time of the 3 cancers mentioned above is higher than the others. The median survival time of other tumors with bone metastases is less than 10 months. In general, survival is worse in patients with digestive system cancer and bone metastases compared with other types of primary cancer. The median survival time in patients with hepatobiliary, gastric, and anal tumors is 3 months. Among patients with pancreatic tumor and bone metastases, the median survival time is 2 months.

Incidence proportion and median survival time of patients with bone metastases, as organized based on the presence or absence of brain, liver, and lung metastases, are shown in *Table 2*. In summary, the incidence of bone metastasis was higher, and survival time was shorter among patients with more extensive metastases at diagnosis. The incidence of bone-only metastasis was 13.98% in NSCLC (NOS/others), 12.64% in SCLC, and 11.81% in ADC. In descending order, patients with bladder cancer (5.14%), SCC (4.90%), esophageal cancer (4.52%), gastric cancer (2.86%), hepatobiliary cancer (2.74%), renal cancer (2.65%), breast cancer (2.22%), and NSCLC (BAC) (2.02%) showed an incidence proportion of bone metastases of >2%. The median survival time among patients with bone-only

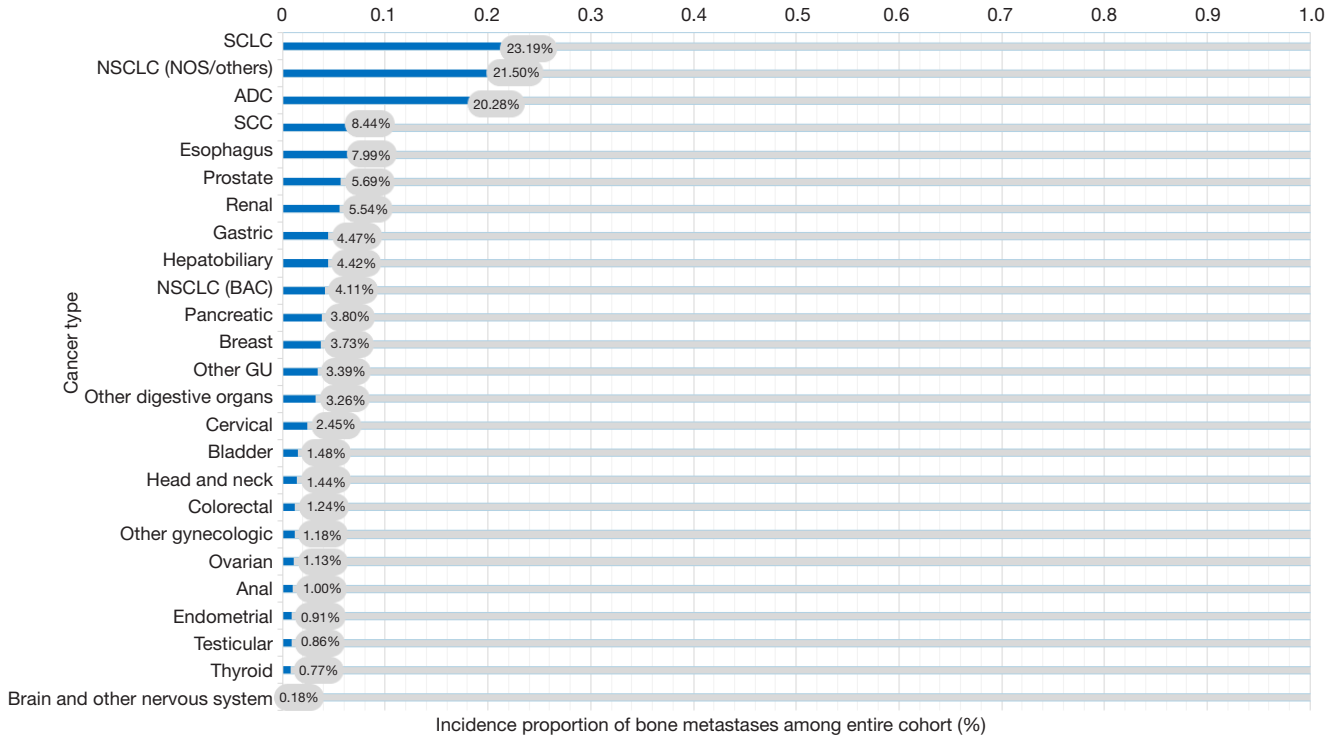

Figure 2 Incidence proportion of patients diagnosed with bone metastases within the entire cohort. SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic.

metastases in thyroid cancer, breast cancer, prostate cancer, and anal cancer was 60, 35, 27, and 20 months, respectively.

For patients with head and neck cancer, the incidence of comorbidity with liver metastases and bone metastasis was 42.47%. Among patients with was cancer, the incidence of comorbidity with liver metastasis and bone metastasis is higher in NSCLC (BAC) (54.17%), ADC (53.73%), and NSCLC (NOS/others) (44.10%) than in SCC (39.59%) and SCLC (37.15%). Furthermore, we found that the incidence of comorbidity of brain metastases and bone metastasis was higher than other sites among patients with digestive system cancer and gynecologic cancer.

Table S1 shows the incidence proportions of patients diagnosed with bone metastases, classified according to primary cancer, age, race, and gender. Median survival estimates, and those of age, race, gender, and cancer type, are displayed in *Table S2*.

Discussion

In our study, we showed the number and incidence proportion of patients with bone metastases and the prognosis of identified bone metastases among patients with cancer of the digestive system with the lowest median survival time. To our knowledge, this is the first epidemiologic study of bone metastases using the entire SEER database. Roodman *et al.* pointed out that the exact prevalence of bone metastasis remains unknown, and patients with bone metastases are usually incurable (21). Therefore, it is probable that our study may have widespread applications and could be useful in the formation of screening paradigms for bone metastases, clinical treatment and trial design, and counseling of different subsets of patients with cancer.

Incidence of bone metastasis

In 1997, Coleman *et al.* reported that the incidence of bone metastasis was 30–40% for patients with lung cancer, which is higher than our results (22). In 2013, Sathiakumar *et al.* reported that the incidence of bone metastasis among lung cancer patients was 19.8%, based on data from 1999 to

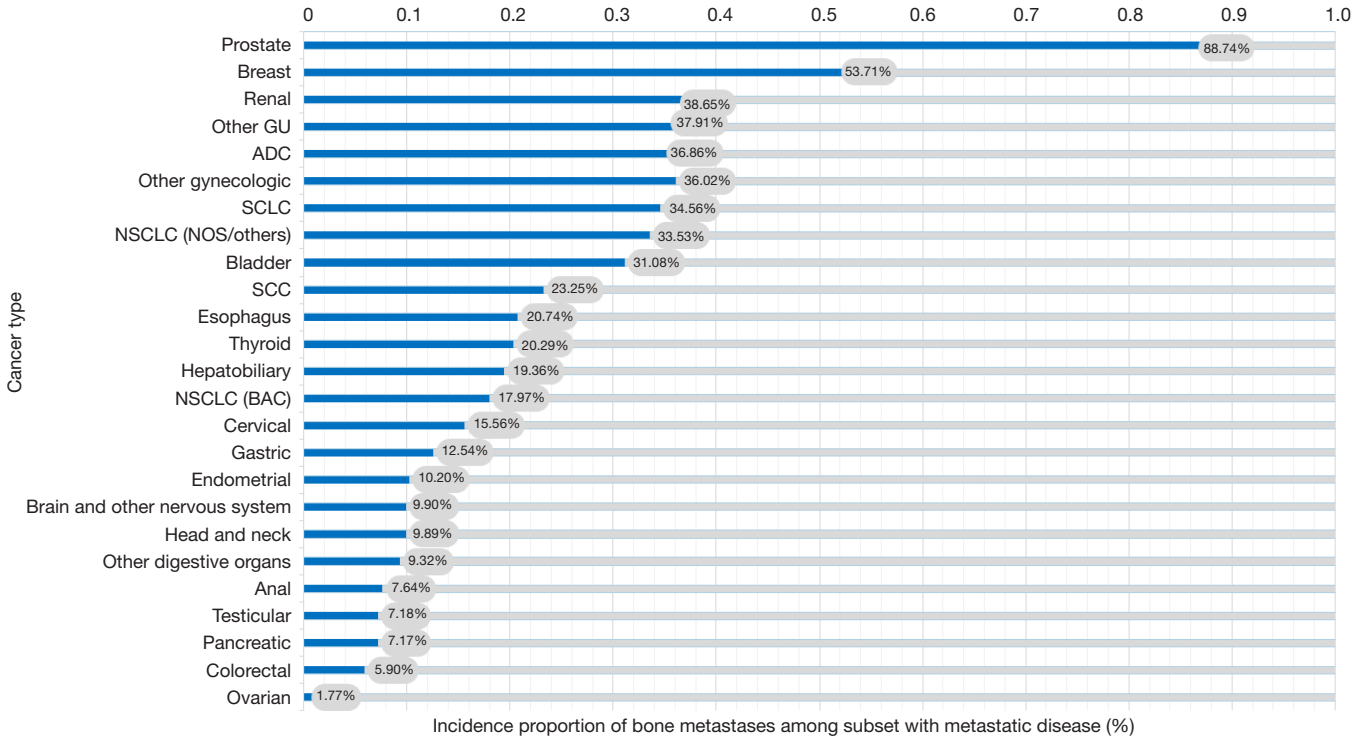

Figure 3 Incidence proportion of patients diagnosed with bone metastases within subset with metastatic disease. SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic.

2006 (23). Al Husaini *et al.* pointed out that the incidence of skeletal metastasis in advanced-stage lung cancer was 30–40% (24).

In our study, we found that the incidence of bone metastases was 16.89% in patients with newly diagnosed lung cancer and 33.10% in patients with metastatic lung cancer. A comparison of our findings with those of other studies confirms that the rate of bone metastasis among lung cancer is gradually decreasing, which has contributed to the popularization of screening and the development of effective treatment strategies. Additionally, we found the incidence of bone metastases among patients with SCLC to be higher than that of patients with non-small cell lung cancer (NSCLC). Yerushalmi *et al.* found that the incidence of bone metastases among patients with breast cancer had decreased steadily over 3 time periods (25) (1989–1991: 7.5%, 1992–1997: 5.3%, 1998–2001: 3.5%). Jensen *et al.* noted that the incidence rate of bone metastases among patients with breast cancer was 3.6% in a population of 35,912 patients (19). In this study, the incidence was slightly lower than that reported by earlier studies. Pietropaoli *et al.* indicated that only approximately 1% of patients with stage IV carcinoma of the head and neck had concomitant bone metastases (26), which is similar to our results.

Previous studies have reported that the incidence rate of bone metastases in patients with hepatocellular carcinoma ranges from 3% to 20% (27,28). These findings are consistent with our results. However, the studies just mentioned above only discussed the incidence rate of bone metastases in single cancers. There is no study which systematically analyzes the incidence of bone metastases in different cancers types. Our study shows that lung cancer is most likely to present with bone metastasis, which may support recent screening guidelines. Previous studies have shown that the incidence rate of bone metastases in metastatic prostate cancer is over 80%, while bone metastases occur in 65–80% of patients with metastatic breast cancer (29-34). Our study also indicates that the incidence proportion of bone metastases is high in patients with breast or prostate cancer. Previous studies have shown that bone metastases occur in approximately 30% of patients with invasive bladder cancer and renal cancer

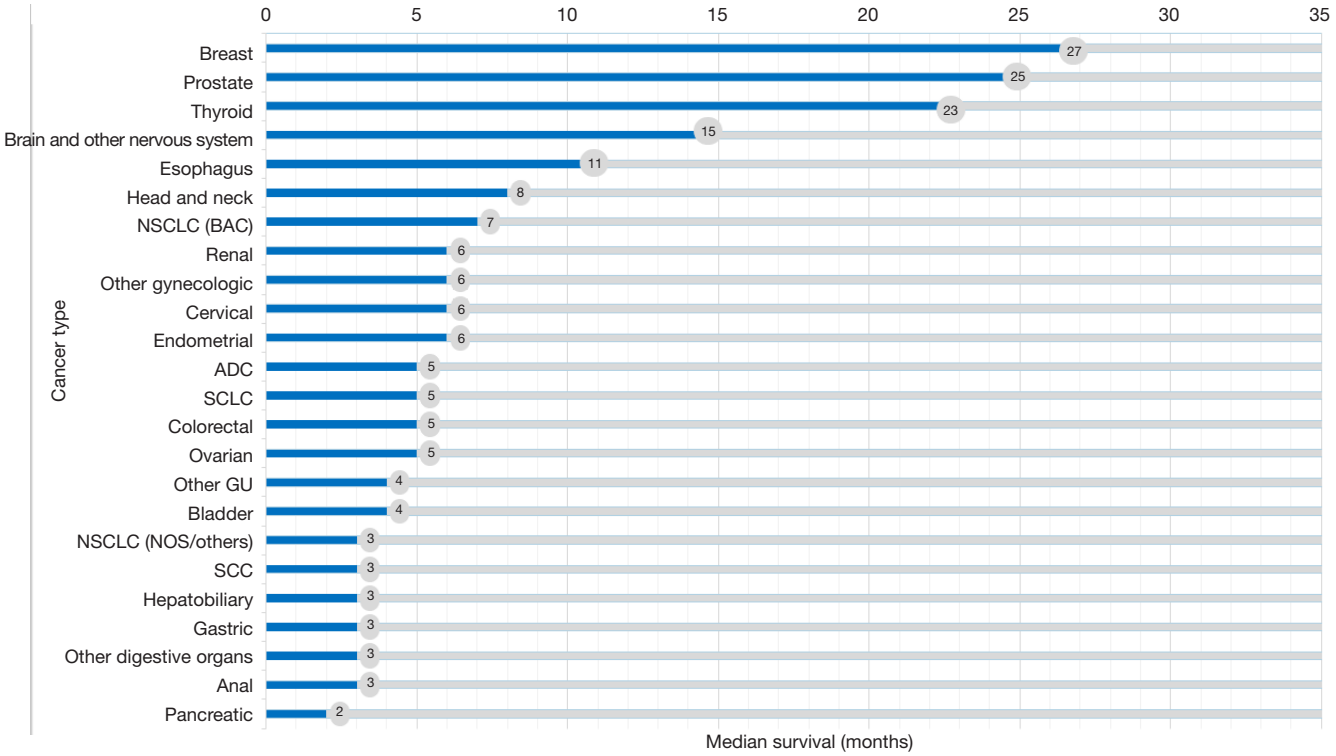

Figure 4 Median survival of patients with identified bone metastases. SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic.

(35-38). In our study, the incidence rate of bone metastases was 16.08% and 1.48% in renal cancer and bladder cancer, respectively. Furthermore, bone metastases accounted for 38.65% and 31.08% of metastatic renal and bladder cancers, respectively. Though the rate of bone metastases is not high in bladder cancer, bone cancer accounts for a relatively large portion of the metastatic sites among patients with metastatic bladder cancer. Therefore, we must pay attention to the screening of bone metastases in this setting.

Survival

Our results show that cancer presented at diagnosis with bone metastases with the longest median survival time is breast cancer (27 months), followed by prostate cancer (25 months), and thyroid cancer (23 months). Previous studies had shown that the median survival time is 30 and 28 months among breast cancer patients with bone metastases and prostate cancer patients with bone metastases (39,40). These results are similar to ours. Bhatia reported that the prognosis of hepatocellular carcinoma with bone metastasis is extremely poor, with a median survival of only 1–2 months (41). We also found that the median survival time is the shortest in cancers of the digestive system. Silvestris *et al.* indicated that the median survival was 6 months in gastric cancer patients after bone metastasis diagnosis (42). Our results showed the median survival is 3 months among gastric cancer patients with bone metastases, which was a little shorter than the earlier study.

Clinical implications

Bone metastases are associated with an increased risk of mortality for patients with cancer and may lead to a poor quality of life (17,43,44). The early detection of bone metastases may minimize morbidity and mortality and lead to a better quality of life (45-47), while also being a fundamental step in anticancer treatment (48-50). The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology also recommended routine screening bone metastases in patients with SCLC, prostatic cancer, and high-metastasis-risk renal cancer (51-54). Our results support

Table 2 Incidence proportion and median survival of patients with bone metastases by extent of systemic disease

Site	Sub-site	Type of systemic metastasis	Number of patients	Number of patients with bone metastases	Proportion with bone metastases (%)	Median survival in months (interquartile range)
Head and neck[1]	Head and neck[1]	Lung	1,284	217	16.90	6 [3–13]
		Liver	372	158	42.47	8 [3–18]
		Brain	77	21	27.27	5 [1–18]
		2 of 3	273	122	44.69	4 [2–12]
		All 3	18	12	66.67	5 [1–13]
		None	75,371	532	0.71	10 [4–23]
Thyroid	Thyroid	Lung	1,076	224	20.82	11 [2–49]
		Liver	95	31	32.63	4 [1–13]
		Brain	48	17	35.42	5 [2–NR]
		2 of 3	142	63	44.37	5 [2–12]
		All 3	8	5	62.50	2 [1–6]
		None	86,987	339	0.39	60 [12–NR]
Breast	Breast	Lung	4,926	2,414	49.01	24 [7–50]
		Liver	3,690	2,042	55.34	18 [4–42]
		Brain	752	418	55.59	15 [4–34]
		2 of 3	2,504	1,692	67.57	11 [2–30]
		All 3	349	280	80.23	4 [1–17]
		None	424,126	9,415	2.22	35 [14–69]
Respiratory system	SCLC	Lung	2,279	523	22.95	6 [1–11]
		Liver	7,849	2,916	37.15	5 [1–9]
		Brain	3,489	580	16.62	5 [2–10]
		2 of 3	3,930	1,710	43.51	4 [1–8]
		All 3	517	299	57.83	3 [1–7]
		None	20,444	2,584	12.64	7 [2–12]
	SCC	Lung	6,065	1,051	17.33	3 [1–7]
		Liver	2,445	968	39.59	3 [1–6]
		Brain	2,354	490	20.82	3 [1–6]
		2 of 3	1,904	832	43.70	2 [1–5]
		All 3	284	160	56.34	2 [1–4]
		None	79,077	3,877	4.90	4 [1–9]

Table 2 (*continued*)

Table 2 (*continued*)

Site	Sub-site	Type of systemic metastasis	Number of patients	Number of patients with bone metastases	Proportion with bone metastases (%)	Median survival in months (interquartile range)
	ADC	Lung	14,485	4,233	29.22	5 [2–14]
		Liver	5,265	2,829	53.73	3 [1–9]
		Brain	11,839	3,357	28.36	5 [2–14]
		2 of 3	8,273	4,402	53.21	3 [1–10]
		All 3	1,353	990	73.17	3 [1–9]
		None	102,527	12,106	11.81	6 [2–15]
	NSCLC (BAC)	Lung	352	38	10.80	11 [4–15]
		Liver	24	13	54.17	2 [1–10]
		Brain	53	15	28.30	10 [3–19]
		2 of 3	55	27	49.09	7 [3–21]
		All 3	3	1	33.33	6 [NA]
		None	3,953	80	2.02	11 [3–23]
	NSCLC (NOS/ others)	Lung	1,881	538	28.60	3 [1–8]
		Liver	1,093	482	44.10	2 [1–7]
		Brain	2,124	485	22.83	3 [1–8]
		2 of 3	1,358	604	44.48	2 [1–5]
		All 3	223	129	57.85	2 [1–4]
		None	13,306	1,860	13.98	4 [1–9]
Digestive system	Esophagus	Lung	1,242	239	19.24	10 [4–42]
		Liver	2,722	505	18.55	10 [3–30]
		Brain	228	58	25.44	9 [4–30]
		2 of 3	1,206	310	25.70	11 [4–43]
		All 3	87	38	43.68	14 [7–NR]
		None	20,470	925	4.52	13 [4–36]
	Gastric	Lung	979	191	19.51	4 [1–7]
		Liver	5,342	406	7.60	3 [1–9]
		Brain	137	34	24.82	3 [1–4]
		2 of 3	1,186	267	22.51	2 [NR–8]
		All 3	52	22	42.31	3 [1–4]
		None	35,874	1,027	2.86	4 [1–9]

Table 2 (*continued*)

Table 2 (*continued*)

Site	Sub-site	Type of systemic metastasis	Number of patients	Number of patients with bone metastases	Proportion with bone metastases (%)	Median survival in months (interquartile range)
	Hepatobiliary	Lung	3,238	472	14.58	2 [0–6]
		Liver	4,598	399	8.68	3 [1–9]
		Brain	125	45	36.00	4 [1–10]
		2 of 3	1,314	298	22.68	2 [1–5]
		All 3	36	17	47.22	2 [0–7]
		None	61,751	1,692	2.74	3 [1–8]
	Pancreatic	Lung	2,846	304	10.68	6 [2–19]
		Liver	23,754	1,140	4.80	5 [1–14]
		Brain	71	16	22.54	2 (1–7)
		2 of 3	5,011	762	15.21	1 [0–4]
		All 3	92	40	43.48	2 [0–3]
		None	42,886	573	1.34	3 [1–9]
	Colorectal	Lung	3,425	261	7.62	6 [2–18]
		Liver	26,849	1,102	4.10	5 [1–14]
		Brain	190	18	9.47	2 [1–7]
		2 of 3	8,472	983	11.60	5 [1–14]
		All 3	205	68	33.17	2 [1–10]
		None	210,132	653	0.31	6 [2–18]
	Anal	Lung	129	11	8.53	6 [5–8]
		Liver	317	26	8.20	9 [4–27]
		Brain	9	1	11.11	NA
		2 of 3	116	15	12.93	4 [1–9]
		All 3	3	0	0.00	NA
		None	11,576	68	0.59	20 [6–36]
	Other digestive organs	Lung	748	122	16.31	2 [1–7]
		Liver	3,714	255	6.87	3 [1–11]
		Brain	66	15	22.73	2 [1–6]
		2 of 3	728	179	24.59	2 [0–5]
		All 3	36	16	44.44	1 [0–2]
		None	18,222	269	1.48	3 [1–11]

Table 2 (*continued*)

Table 2 (*continued*)

Site	Sub-site	Type of systemic metastasis	Number of patients	Number of patients with bone metastases	Proportion with bone metastases (%)	Median survival in months (interquartile range)
Genitourinary	Renal	Lung	5,624	1,605	28.54	6 [2–15]
		Liver	1,237	372	30.07	3 [1–9]
		Brain	449	137	30.51	5 [2–15]
		2 of 3	2,360	949	40.21	3 [1–8]
		All 3	219	118	53.88	3 [1–7]
		None	91,232	2,422	2.65	10 [3–30]
	Bladder	Lung	1,437	1,131	78.71	4 [1–10]
		Liver	660	485	73.48	2 [1–6]
		Brain	184	154	83.70	2 [1–11]
		2 of 3	359	286	79.67	2 [1–5]
		All 3	24	19	79.17	1 [0–2]
		None	344,200	17,675	5.14	5 [2–12]
	Prostate	Lung	1,133	191	16.86	20 [8–47]
		Liver	497	148	29.78	10 [4–22]
		Brain	724	68	9.39	10 [3–24]
		2 of 3	1,185	345	29.11	9 [3–24]
		All 3	347	164	47.26	14 [4–NR]
		None	277,125	296	0.11	27 [11–57]
	Testicular	Lung	883	44	4.98	NR [8–NR]
		Liver	87	12	13.79	9 [7–19]
		Brain	14	1	7.14	NA
		2 of 3	261	30	11.49	13 [4–NR]
		All 3	56	8	14.29	8 [0–NR]
		None	15,360	48	0.31	NR [8–NR]
	Other GU	Lung	217	48	22.12	5 [2–12]
		Liver	155	50	32.26	2 [0–6]
		Brain	14	5	35.71	4 [1–7]
		2 of 3	110	44	40.00	1 [0–6]
		All 3	4	0	0.00	NA
		None	7,967	140	1.76	7 [2–11]

Table 2 (*continued*)

Table 2 (*continued*)

Site	Sub-site	Type of systemic metastasis	Number of patients	Number of patients with bone metastases	Proportion with bone metastases (%)	Median survival in months (interquartile range)
Gynecologic	Ovarian	Lung	1,515	60	3.96	4 [1–19]
		Liver	1,928	72	3.73	2 [0–11]
		Brain	56	10	17.86	NR [NR–10]
		2 of 3	650	88	13.54	4 [1–9]
		All 3	17	8	47.06	2 [NR–6]
		None	33,302	184	0.55	7 [1–34]
	Endometrial	Lung	1,898	225	11.85	7 [2–18]
		Liver	638	66	10.34	6 [2–15]
		Brain	87	15	17.24	2 [2–6]
		2 of 3	593	156	26.31	3 [1–9]
		All 3	36	18	50.00	3 [1–10]
		None	89,897	337	0.37	8 [2–19]
	Cervical	Lung	702	116	16.52	6 [3–13]
		Liver	250	63	25.20	6 [2–11]
		Brain	35	15	42.86	3 [1–6]
		2 of 3	259	103	39.77	4 [1–9]
		All 3	8	5	62.50	3 [1–10]
		None	21,514	256	1.19	10 [4–20]
	Other gynecologic	Lung	457	47	10.28	4 [1–10]
		Liver	187	17	9.09	6 [3–14]
		Brain	9	1	11.11	2 [2–2]
		2 of 3	137	17	12.41	2 [0–5]
		All 3	13	3	23.08	1 [NR]
		None	14,357	94	0.65	8 [3–22]
Brain and other nervous system	Brain and other nervous system	Lung	32	4	12.50	19 [3–NR]
		Liver	14	4	28.57	1 [NR–8]
		Brain	200	4	2.00	3 [NR]
		2 of 3	9	2	22.22	4 [NR–8]
		All 3	NA	NA	NA	NA
		None	32,872	45	0.14	16 [2–NR]

[1], lip, tongue, gum, floor of mouth, & other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle & inner ear, larynx, trachea, orbit & lacrimal gland, retina, eyeball, eye, NOS. GI, gastrointestinal; GU, genitourinary; GYN, gynecologic; SCLC, small-cell lung; NSCLC (NOS/others), non-small cell lung cancer not otherwise specified or non-small cell lung cancer other lung cancer; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung; NSCLC (BAC), bronchioloalveolar carcinoma; NR, not reached; NA, not applicable.

the current guidelines as these cancers are all at high risk of the development of bone metastases, although the routine use of bone screening is not recommended in NSCLC. Our data showed that the incidence of bone metastases at diagnosis in NSLCLC is relatively high. Therefore, in patients with a diagnosis of stage IV NSCLC, special focus should be dedicated to the screening of the bones.

Furthermore, screening of bone metastases is not routinely performed for patients with esophagus cancer (55). However, our data revealed a 7.99% and 20.74% incidence proportion of bone metastases in patients with esophagus cancer and metastatic esophagus cancer, respectively. Therefore, routine screening of bone metastases is necessary for patients with these cancers.

As screening was not routinely performed in these patients, bone metastases are always discovered only as a result of SREs, which may be a more advanced disease that shortens survival (56) and often requires surgical intervention or a more complex treatment plan. However, surgery for pathological fracture and loss of motor function and mobility might also increase mortality (5). Our data show a relatively high rate of bone metastasis in these populations—one which may be underestimated. Therefore, our findings may support the need to routinely screen for bone metastases at diagnosis for these patients.

As for patients with head and neck cancers, the incidence of comorbidity for liver metastasis and bone metastases is high. Patients with breast and bladder cancer have a high incidence of comorbidity with bone metastasis and brain, liver, or lung metastasis. Therefore, a diagnosis of bone metastases may be a strong signal that other sites of metastases may exist in patients. For lung cancer, we should pay attention to the comorbidity of bone metastases and liver metastases, while for digestive system cancer and gynecologic cancer, we may be more concerned about the comorbidity of bone metastases and brain metastases.

Previous studies have shown that patients with bone-only metastases have a better prognosis (57-59). For instance, previous investigators pointed out that the median survival time of patients with breast cancer and bone-only metastasis was about 20–50 months, which is much longer than multiple sites metastasis (60-63). This result is consistent with our findings. The incidence of bone-only metastasis is high in NSCLC (NOS/others), SCLC, ADC, bladder cancer, and esophageal cancer. So, for patients with these cancers, we must find a specific metastasis status. Because the treatment of bone-only metastasis is different from other sites or multiple sites metastasis (60), identifying bone-only metastasis may help clarify the clinical course, improve the prognosis for patients with bone-only metastasis, and estimate median survival time more accurately (64,65).

Our data also have value for the design of clinical trials. The data in our study may help investigators quantify the specific number of patients needed to be excluded from the trial enrollment, with bone metastasis as an exclusion criterion. Moreover, for studies or trials which are related to bone metastases, our study can provide generalizable estimates of incidence and prognosis for use in calculations and some trial design.

Limitations

The present study has some potential limitations. Firstly, we only identified bone metastases at initial cancer diagnosis, and, because SEER cannot provide information relating to disease recurrence, we could not screen patients with bone metastases after initial diagnosis. Secondly, we do not have information relating to the number size and exact location of the bone metastases. Thirdly, screening was not conducted across all malignancies, and therefore some data of metastases might have been missed. Finally, treatment information for the metastatic sites was not provided, so we could not study the treatment received by each patient.

Although this study has several limitations, it provides new information regarding the epidemiology of bone metastasis. Incidence of bone metastasis and the specific proportion of patients with bone metastases among different cancer types could help in the development of the formation of screening paradigms for bone metastases, clinical treatment and trial design, and counseling of different subsets of patients with cancer.

Conclusions

The results of this study provide population-based estimates of the incidence of bone metastasis and the specific incidence proportion of patients with bone metastasis diagnosis of solid tumors. We have shown that prostate cancer and breast cancer are most likely to occur with bone metastases. Additionally, the rate of bone metastasis was more than 20% in patients with lung, renal, bladder, thyroid, and esophageal cancers. We also found that the median survival time was more than 20 months in bone metastatic breast cancer, prostate cancer, and thyroid cancer. Conversely, the median survival time was the shortest in gastrointestinal, lung, and gynecologic cancer

with bone metastases. These data may help clinicians in their justification of using of bone screening, which may also have an important role in clinical trial design and better prognosis. The findings can support the decision of screening of the bone and extracranial metastases for patients with high-risk primary malignancy.

Acknowledgments

Funding: This work was funded by the National Natural Science Foundation of China (No. 81501933), the Zhejiang Provincial Medical and Health Technology Foundation of China (No. 2018KY129), Wenzhou Leading Innovative Talent Project (No. RX2016004) and the Wenzhou Municipal Science and Technology Bureau (No. Y20170389). The funders had no role in the design, execution, or writing of the study.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.55). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Ruatta F, Derosa L, Escudier B, et al. Prognosis of renal cell carcinoma with bone metastases: Experience from a large cancer centre. Eur J Cancer 2019;107:79-85.
2. Qiu MZ, Shi SM, Chen ZH, et al. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. Cancer Med 2018;7:3662-72.
3. Tahara RK, Brewer TM, Theriault RL, et al. Bone Metastasis of Breast Cancer. Adv Exp Med Biol 2019;1152:105-29.
4. Suva LJ, Washam C, Nicholas RW, et al. Bone metastasis: mechanisms and therapeutic opportunities. Nat Rev Endocrinol 2011;7:208-18.
5. Norgaard M, Jensen AO, Jacobsen JB, et al. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). J Urol 2010;184:162-7.
6. Hernandez RK, Wade SW, Reich A, et al. Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. BMC Cancer 2018;18:44.
7. Tanaka R, Yonemori K, Hirakawa A, et al. Risk Factors for Developing Skeletal-Related Events in Breast Cancer Patients With Bone Metastases Undergoing Treatment With Bone-Modifying Agents. Oncologist 2016;21:508-13.
8. Santoni M, Conti A, Procopio G, et al. Bone metastases in patients with metastatic renal cell carcinoma: are they always associated with poor prognosis? J Exp Clin Cancer Res 2015;34:10.
9. Santini D, Procopio G, Porta C, et al. Natural history of malignant bone disease in renal cancer: final results of an Italian bone metastasis survey. PLoS One 2013;8:e83026.
10. Guo Q, Zhang C, Guo X, et al. Incidence of bone metastasis and factors contributing to its development and prognosis in newly diagnosed renal cell carcinoma: a population-based study. Cancer Manag Res 2018;10:2935-44.
11. Nguyen QN, Chun SG, Chow E, et al. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients With Predominantly Nonspine Bone Metastases: A Randomized Phase 2 Trial. JAMA Oncol 2019;5:872-8.
12. Escudier B, Powles T, Motzer RJ, et al. Cabozantinib, a New Standard of Care for Patients With Advanced Renal Cell Carcinoma and Bone Metastases? Subgroup Analysis of the METEOR Trial. J Clin Oncol 2018;36:765-72.
13. Weilbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. Nat Rev Cancer 2011;11:411-25.
14. Ell B, Kang Y. SnapShot: Bone Metastasis. Cell 2012;151:690-690.e1.
15. Maurizi A, Rucci N. The Osteoclast in Bone Metastasis: Player and Target. Cancers (Basel) 2018. doi: 10.3390/cancers10070218.

16. Umer M, Mohib Y, Atif M, et al. Skeletal metastasis in renal cell carcinoma: A review. Ann Med Surg (Lond) 2018;27:9-16.
17. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165-76.
18. Hage WD, Aboulafia AJ, Aboulafia DM. Incidence, location, and diagnostic evaluation of metastatic bone disease. Orthop Clin North Am 2000;31:515-28, vii.
19. Jensen AO, Jacobsen JB, Norgaard M, et al. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer 2011;11:29.
20. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2012), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.
21. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655-64.
22. Coleman RE. Skeletal complications of malignancy. Cancer 1997;80:1588-94.
23. Sathiakumar N, Delzell E, Morrisey MA, et al. Mortality following bone metastasis and skeletal-related events among patients 65 years and above with lung cancer: A population-based analysis of U.S. Medicare beneficiaries, 1999-2006. Lung India 2013;30:20-6.
24. Al Husaini H, Wheatley-Price P, Clemons M, et al. Prevention and management of bone metastases in lung cancer: a review. J Thorac Oncol 2009;4:251-9.
25. Yerushalmi R, Woods R, Kennecke H, et al. Patterns of relapse in breast cancer: changes over time. Breast Cancer Res Treat 2010;120:753-9.
26. Pietropaoli MP, Damron TA, Vermont AI. Bone metastases from squamous cell carcinoma of the head and neck. J Surg Oncol 2000;75:136-41.
27. Attili VS, Babu KG, Lokanatha D, et al. Bone metastasis in hepatocellular carcinoma: need for reappraisal of treatment. J Cancer Res Ther 2008;4:93-4.
28. Okazaki N, Yoshino M, Yoshida T, et al. Bone metastasis in hepatocellular carcinoma. Cancer 1985;55:1991-4.
29. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 1987;55:61-6.
30. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
31. Pezaro C, Omlin A, Lorente D, et al. Visceral disease in castration-resistant prostate cancer. Eur Urol 2014;65:270-3.
32. Halabi S, Kelly WK, Ma H, et al. Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer. J Clin Oncol 2016;34:1652-9.
33. Body JJ, Quinn G, Talbot S, et al. Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases. Crit Rev Oncol Hematol 2017;115:67-80.
34. Yanae M, Fujimoto S, Tane K, et al. Increased risk of SSEs in bone-only metastatic breast cancer patients treated with zoledronic acid. J Bone Oncol 2017;8:18-22.
35. Wallmeroth A, Wagner U, Moch H, et al. Patterns of metastasis in muscle-invasive bladder cancer (pT2-4): An autopsy study on 367 patients. Urol Int 1999;62:69-75.
36. Woodward E, Jagdev S, McParland L, et al. Skeletal complications and survival in renal cancer patients with bone metastases. Bone 2011;48:160-6.
37. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.
38. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
39. Gong Y, Zhang J, Ji P, et al. Incidence proportions and prognosis of breast cancer patients with bone metastases at initial diagnosis. Cancer Med 2018;7:4156-69.
40. Teoh JY, Tsu JH, Yuen SK, et al. Prognostic significance of time to prostate-specific antigen (PSA) nadir and its relationship to survival beyond time to PSA nadir for prostate cancer patients with bone metastases after primary androgen deprivation therapy. Ann Surg Oncol 2015;22:1385-91.
41. Bhatia R, Ravulapati S, Befeler A, et al. Hepatocellular Carcinoma with Bone Metastases: Incidence, Prognostic Significance, and Management-Single-Center Experience. J Gastrointest Cancer 2017;48:321-5.
42. Silvestris N, Pantano F, Ibrahim T, et al. Natural history of malignant bone disease in gastric cancer: final results of a multicenter bone metastasis survey. PLoS One 2013;8:e74402.
43. Diel IJ. Effectiveness of bisphosphonates on bone pain and quality of life in breast cancer patients with metastatic bone disease: a review. Support Care Cancer 2007;15:1243.
44. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab

versus zoledronic acid. Clin Cancer Res 2012;18:4841-9.
45. Weinfurt KP, Castel LD, Li Y, et al. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Med Care 2004;42:164-75.
46. Pockett RD, Castellano D, McEwan P, et al. The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain. Eur J Cancer Care (Engl) 2010;19:755-60.
47. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584-93.
48. Gravel G, Tselikas L, Moulin B, et al. Early detection with MRI of incomplete treatment of spine metastases after percutaneous cryoablation. Eur Radiol 2019;29:5655-63.
49. Onoue K, Nishio M, Yakami M, et al. CT temporal subtraction improves early detection of bone metastases compared to SPECT. Eur Radiol 2019;29:5673-81.
50. Hirai T, Shinoda Y, Tateishi R, et al. Early detection of bone metastases of hepatocellular carcinoma reduces bone fracture and paralysis. Jpn J Clin Oncol 2019;49:529-36.
51. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 2.2018. Available online: https://www.nccn.org/
52. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 2.2018. Available online: https://www.nccn.org/
53. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Squamous Cell Skin Cancer. Version 2.2018. Available online: https://www.nccn.org/
54. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 3.2016. Available online: https://www.nccn.org/
55. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers. Version 1.2017. Available online: https://www.nccn.org/
56. Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol 2002;168:1005-7.
57. Soran A, Ozmen V, Ozbas S, et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol 2018;25:3141-9.
58. Lee SJ, Park S, Ahn HK, et al. Implications of bone-only metastases in breast cancer: favorable preference with excellent outcomes of hormone receptor positive breast cancer. Cancer Res Treat 2011;43:89-95.
59. Shen L, Dong J, Li S, et al. M1 stage subdivision and treatment outcome of patients with bone-only metastasis of nasopharyngeal carcinoma. Oncologist 2015;20:291-8.
60. Niikura N, Liu J, Hayashi N, et al. Treatment outcome and prognostic factors for patients with bone-only metastases of breast cancer: a single-institution retrospective analysis. Oncologist 2011;16:155-64.
61. Domchek SM, Younger J, Finkelstein DM, et al. Predictors of skeletal complications in patients with metastatic breast carcinoma. Cancer 2000;89:363-8.
62. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. Br J Cancer 1998;77:336-40.
63. Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer. implications for management. Eur J Cancer 2000;36:476-82.
64. Sun XS, Liang YJ, Liu SL, et al. Subdivision of Nasopharyngeal Carcinoma Patients with Bone-Only Metastasis at Diagnosis for Prediction of Survival and Treatment Guidance. Cancer Res Treat 2019;51:1259-68.
65. He S, Wang Y, Peng H, et al. Pretreatment Alkaline Phosphatase and Epstein-Barr Virus DNA Predict Poor Prognosis and Response to Salvage Radiotherapy in Patients with Nasopharyngeal Carcinoma and Metachronous Bone-Only Metastasis. J Cancer 2017;8:417-24.

Cite this article as: Huang JF, Shen J, Li X, Rengan R, Silvestris N, Wang M, Derosa L, Zheng X, Belli A, Zhang XL, Li YM, Wu A. Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study. Ann Transl Med 2020;8(7):482. doi: 10.21037/atm.2020.03.55

Supplementary

Table S1 Incidence proportion of patients with identified bone metastases at diagnosis by primary cancer site as stratified by age, race, and gender

		Age					Race					Gender					
Site	Sub-site	Age category in years	Number of patients with bone metastases	Entire cohort	Incidence proportion of bone metastases among entire cohort (%)	Incidence proportion of bone metastases among subset with metastatic disease (%)	Race	Number of patients with bone metastases	Entire cohort	Incidence proportion of bone metastases among entire cohort (%)	Incidence proportion of bone metastases among subset with metastatic disease (%)	Gender	Number of patients with brain metastases (total number of patients in subcategory)	Number of entire cohort	Number of metastatic disease	Incidence proportion of brain metastases among entire cohort	Incidence proportion of brain metastases among subset with metastatic disease
Head and neck	Head and neck[1]	18–40	57	3,399	1.68	18.69	White	819	59,043	1.39	9.55	Male	780	54,314	7,862	1.44	9.92
		41–60	395	29,942	1.32	8.73	Black	103	6,300	1.63	11.12	Female	334	23,296	3,405	1.43	9.81
		61–80	522	36,216	1.44	9.53	Hispanic	99	6,062	1.63	12.04						
		>80	96	8,053	1.19	10.00	Asian or Pacific Islander	80	5,093	1.57	10.99						
							American Indian/ Alaska Native	5	480	1.04	7.81						
							Unknown	8	632	1.27	8.99						
Thyroid	Thyroid	18–40	37	24,002	0.15	9.16	White	380	57,307	0.66	19.84	Male	309	21,708	1,427	1.42	21.65
		41–60	186	39,558	0.47	19.79	Black	103	6,109	1.69	34.92	Female	370	66,648	1,920	0.56	19.27
		61–80	370	22,434	1.65	24.25	Hispanic	92	14,305	0.64	13.61						
		>80	86	2,362	3.64	18.03	Asian or Pacific Islander	100	9,179	1.09	23.75						
							American Indian/ Alaska Native	3	532	0.56	11.11						
							Unknown	1	924	0.11	7.69						
Breast	Breast	18–40	1,140	24,616	4.63	50.11	White	10,908	298,403	3.66	55.70	Male	210	3,414	335	6.15	62.69
		41–60	6,294	176,055	3.58	52.34	Black	2,447	48,090	5.09	50.19	Female	16,051	432,933	29,981	3.71	53.54
		61–80	7,022	194,444	3.61	56.07	Hispanic	1,707	48,576	3.51	48.72						
		>80	1,805	41,232	4.38	51.69	Asian or Pacific Islander	1,067	36,476	2.93	51.37						
							American Indian/ Alaska Native	85	2,392	3.55	47.22						
							Unknown	47	2,410	1.95	48.45						
Respiratory system	Small cell	18–40	25	115	21.74	34.72	White	7,793	32,785	23.77	35.42	Male	5,103	19,710	13,736	25.89	37.15
		41–60	2,320	9,373	24.75	35.73	Black	714	3,547	20.13	29.86	Female	4,120	20,059	12,950	20.54	31.81
		61–80	6,070	25,894	23.44	35.34	Hispanic	399	1,823	21.89	32.28						
		>80	808	4,387	18.42	27.45	Asian or Pacific Islander	271	1,348	20.10	30.08						
							American Indian/ Alaska Native	42	230	18.26	29.37						
							Unknown	4	36	11.11	25.00						
	Squamous cell carcinoma	18–40	32	441	7.26	19.05	White	5,869	71,748	8.18	22.49	Male	5,351	61,490	22,226	8.70	24.08
		41–60	1,615	18,183	8.88	24.13	Black	1,107	11,761	9.41	25.89	Female	2,516	31,750	11,617	7.92	21.66
		61–80	5,100	60,633	8.41	23.33	Hispanic	440	5,281	8.33	22.94						
		>80	1,120	13,983	8.01	21.87	Asian or Pacific Islander	402	3,696	10.88	30.99						
							American Indian/ Alaska Native	41	556	7.37	21.35						
							Unknown	8	198	4.04	11.76						
	Adenocarcinoma	18–40	345	1,109	31.11	44.92	White	21,226	107,687	19.71	37.07	Male	16,070	76,262	41,174	21.07	39.03
		41–60	7,992	32,581	24.53	39.62	Black	3,373	16,920	19.93	33.42	Female	13,776	70,932	39,807	19.42	34.61
		61–80	17,748	90,582	19.59	37.44	Hispanic	2,122	9,477	22.39	37.54						
		>80	3,761	22,922	16.41	29.75	Asian or Pacific Islander	2,961	12,234	24.20	39.50						
							American Indian/ Alaska Native	133	626	21.25	35.75						
							Unknown	41	280	14.64	36.94						
	Bronchioloalveolar adenocarcinoma	18–40	3	29	10.34	27.27	White	123	3,383	3.64	16.97	Male	96	1,701	585	5.64	16.41
		41–60	38	657	5.78	25.85	Black	23	380	6.05	21.10	Female	88	2,774	439	3.17	20.05
		61–80	111	2,935	3.78	17.62	Hispanic	15	308	4.87	18.07						
		>80	32	854	3.75	13.56	Asian or Pacific Islander	23	391	5.88	21.50						
							American Indian/ Alaska Native	0	8	0.00	0.00						
							Unknown	0	5	0.00	0.00						
	Non-small cell and other	18–40	30	102	29.41	38.96	White	3,297	15,419	21.38	34.00	Male	2,681	11,654	7,699	23.00	34.82
		41–60	1,163	4,471	26.01	35.49	Black	522	2,733	19.10	29.03	Female	1,758	8,968	5,525	19.60	31.82
		61–80	2,631	12,521	21.01	33.47	Hispanic	310	1,977	15.68	36.56						
		>80	615	3,528	17.43	30.60	Asian or Pacific Islander	291	1,119	26.01	36.28						
							American Indian/ Alaska Native	14	119	11.76	22.58						
							Unknown	5	35	14.29	27.78						
Digestive system	Esophagus	18–40	29	279	10.39	21.80	White	1,626	19,952	8.15	21.28	Male	1,788	20,367	8,211	8.78	21.78
		41–60	703	6,829	10.29	22.55	Black	197	2,584	7.62	19.13	Female	287	5,588	1,749	5.14	16.41
		61–80	1,142	15,024	7.60	20.19	Hispanic	157	2,009	7.81	19.48						
		>80	201	3,823	5.26	18.31	Asian or Pacific Islander	73	1,181	6.18	16.74						
							American Indian/ Alaska Native	22	165	13.33	28.95						
							Unknown	0	64	0.00	0.00						
	Gastric	18–40	130	1,696	7.67	15.31	White	1,114	23,122	4.82	13.51	Male	1,283	26,580	10,021	4.83	12.80
		41–60	674	11,615	5.80	14.09	Black	198	5,931	3.34	9.56	Female	664	16,990	5,504	3.91	12.06
		61–80	936	22,168	4.22	12.25	Hispanic	374	8,099	4.62	11.84						
		>80	207	8,091	2.56	9.19	Asian or Pacific Islander	239	5,889	4.06	12.71						
							American Indian/ Alaska Native	20	371	5.39	13.42						
							Unknown	2	158	1.27	9.09						
	Hepatobiliary	18–40	44	1,085	4.06	12.68	White	1,816	38,991	4.66	19.67	Male	2,365	47,281	9,859	5.00	23.99
		41–60	1,104	22,942	4.81	21.48	Black	441	8,931	4.94	20.89	Female	821	24,734	6,595	3.32	12.45
		61–80	1,735	38,658	4.49	19.53	Hispanic	544	13,552	4.01	18.39						
		>80	303	9,330	3.25	14.54	Asian or Pacific Islander	345	9,585	3.60	17.48						
							American Indian/ Alaska Native	37	773	4.79	23.13						
							Unknown	3	183	1.64	15.00						
	Pancreatic	18–40	41	1,119	3.66	8.69	White	1,947	51,673	3.77	7.18	Male	1,695	38,321	20,973	4.42	8.08
		41–60	727	16,856	4.31	7.77	Black	327	9,028	3.62	6.41	Female	1,176	36,339	18,562	3.24	6.34
		61–80	1,691	41,976	4.03	7.49	Hispanic	301	7,957	3.78	7.00						
		>80	376	14,709	2.56	5.27	Asian or Pacific Islander	238	5,454	4.36	8.66						
							American Indian/ Alaska Native	19	406	4.68	8.60						
							Unknown	3	142	2.11	5.26						
	Colorectal	18–40	131	9,175	1.43	5.76	White	1,969	166,744	1.18	5.76	Male	1,878	130,273	27,775	1.44	6.76
		41–60	1,023	76,643	1.33	5.77	Black	468	30,329	1.54	6.18	Female	1,207	119,000	24,536	1.01	4.92
		61–80	1,459	117,593	1.24	6.15	Hispanic	371	28,276	1.31	6.13						
		>80	472	45,862	1.03	5.49	Asian or Pacific Islander	244	20,419	1.19	6.08						
							American Indian/ Alaska Native	27	1,850	1.46	6.35						
							Unknown	6	1,654	0.36	8.00						
	Anal	18–40	2	371	0.54	3.92	White	84	9,268	0.91	7.25	Male	53	4,481	524	1.18	10.11
		41–60	52	5,328	0.98	7.69	Black	17	1,344	1.26	9.24	Female	68	7,669	1,060	0.89	6.42
		61–80	56	5,184	1.08	8.05	Hispanic	10	1,097	0.91	6.25						
		>80	11	1,267	0.87	6.83	Asian or Pacific Islander	9	311	2.89	14.06						
							American Indian/ Alaska Native	1	65	1.54	7.14						
							Unknown	0	65	0.00	0.00						
	Other GI	18–40	21	875	2.40	7.75	White	595	15,935	3.73	10.54	Male	344	10,793	3,542	3.19	9.71
		41–60	237	7,051	3.36	9.84	Black	103	3,324	3.10	9.82	Female	512	12,720	4,687	4.03	10.92
		61–80	457	12,285	3.72	10.36	Hispanic	95	2,624	3.62	10.16						
		>80	141	3,302	4.27	12.40	Asian or Pacific Islander	50	1,379	3.63	9.51						
							American Indian/ Alaska Native	10	142	7.04	16.95						
							Unknown	3	109	2.75	20.00						
Genitourinary	Renal	18–40	128	4,916	2.60	37.21	White	3,921	68,184	5.75	39.25	Male	3,820	64,350	9,683	5.94	39.45
		41–60	1,740	35,278	4.93	38.70	Black	557	12,112	4.60	38.23	Female	1,783	36,771	4,815	4.85	37.03
		61–80	2,976	51,015	5.83	39.42	Hispanic	755	14,206	5.31	36.90						
		>80	759	9,912	7.66	36.01	Asian or Pacific Islander	315	5,234	6.02	37.54						
							American Indian/ Alaska Native	51	885	5.76	34.93						
							Unknown	4	500	0.80	19.05						
	Bladder	18–40	15	1,296	1.16	26.79	White	1,423	102,014	1.39	31.54	Male	1,390	94,809	4,167	1.47	33.36
		41–60	385	20,264	1.90	33.92	Black	171	7,255	2.36	28.31	Female	450	29,470	1,754	1.53	25.66
		61–80	1,029	71,202	1.45	31.08	Hispanic	143	7,846	1.82	27.88						
		>80	411	31,517	1.30	28.96	Asian or Pacific Islander	88	5,196	1.69	35.48						
							American Indian/ Alaska Native	14	415	3.37	35.90						
							Unknown	1	1,553	0.06	20.00						
	Prostate	18–40	14	327	4.28	73.68	White	12,788	234,522	5.45	88.66	Male	19,750	346,844	22,257	5.69	88.74
		41–60	3,321	93,062	3.57	87.44	Black	3,396	53,642	6.33	88.92	Female	0	0	0	0	0
		61–80	11,230	229,600	4.89	88.33	Hispanic	2,213	32,440	6.82	88.56						
		>80	5,185	23,855	21.74	90.54	Asian or Pacific Islander	1,119	16,142	6.93	89.88						
							American Indian/ Alaska Native	135	1,316	10.26	88.82						
							Unknown	99	8,782	1.13	83.90						
	Testicular	18–40	87	11,893	0.73	6.14	White	89	11,001	0.81	7.60	Male	143	16,661	1,993	0.86	7.18
		41–60	42	4,119	1.02	8.79	Black	10	506	1.98	12.99	Female	0	0	0	0	0
		61–80	14	594	2.36	15.56	Hispanic	38	1,959	1.94	5.99						
		>80	0	55	0.00	0.00	Asian or Pacific Islander	4	712	0.56	5.13						
							American Indian/ Alaska Native	1	180	0.56	3.45						
							Unknown	1	303	0.33	25.00						
	Other GU	18–40	6	158	3.80	60.00	White	207	6,130	3.38	37.57	Male	199	6,610	507	3.01	39.25
		41–60	40	1,574	2.54	31.01	Black	25	703	3.56	41.67	Female	88	1,857	250	4.74	35.20
		61–80	153	4,625	3.31	37.59	Hispanic	27	977	2.76	31.03						
		>80	88	2,110	4.17	41.71	Asian or Pacific Islander	26	549	4.74	46.43						
							American Indian/ Alaska Native	2	41	4.88	66.67						
							Unknown	0	67	0.00	0.00						
Gynecologic	Ovarian	18–40	25	2,872	0.87	2.44	White	278	25,567	1.09	1.67	Male	0	0	0	0	0
		41–60	121	14,266	0.85	1.51	Black	61	3,270	1.87	2.73	Female	422	37468	23890	1.13	1.77
		61–80	202	16,029	1.26	1.73	Hispanic	49	5,073	0.97	1.64						
		>80	74	4,301	1.72	2.30	Asian or Pacific Islander	33	3,209	1.03	1.84						
							American Indian/ Alaska Native	1	220	0.45	0.70						
							Unknown	0	129	0.00	0.00						
	Endometrial	18–40	17	3,935	0.43	6.34	White	327	12,015	2.72	16.93	Male	0	0	0	0	0
		41–60	320	36,826	0.87	11.29	Black	93	3,084	3.02	15.25	Female	847	93149	8304	0.91	10.20
		61–80	436	46,037	0.95	9.80	Hispanic	88	5,164	1.70	12.48						
		>80	74	6,351	1.17	9.81	Asian or Pacific Islander	47	2,124	2.21	15.67						
							American Indian/ Alaska Native	3	208	1.44	8.57						
							Unknown	0	179	0.00	0.00						
	Cervical	18–40	75	6,351	1.18	15.66	White	120	120	100.00	33.06	Male	0	0	0	0	0
		41–60	163	10,523	1.55	9.61	Black	22	1,347	1.63	47.83	Female	558	22,774	3,585	2.45	15.56
		61–80	190	4,993	3.81	15.93	Hispanic	22	1,522	1.45	37.29						
		>80	30	907	3.31	13.95	Asian or Pacific Islander	13	751	1.73	59.09						
							American Indian/ Alaska Native	1	104	0.96	16.67						
							Unknown	1	112	0.89	100.00						
	Other GYN	18–40	7	736	0.95	36.84	White	41	24,834	0.17	10.35	Male	0	0	0	0	0
		41–60	49	4,491	1.09	33.11	Black	4	2,054	0.19	8.70	Female	179	15160	497	1.18	36.02
		61–80	97	7,085	1.37	46.86	Hispanic	12	4,109	0.29	11.88						
		>80	26	2,848	0.91	21.14	Asian or Pacific Islander	2	1,858	0.11	4.26						
							American Indian/ Alaska Native	0	144	0.00	0.00						
							Unknown	0	128	0.00	0.00						
Brain and other nervous system	Brain and other nervous system	18–40	10	5,505	0.18	10.10	White	380	57,307	0.66	19.84	Male	29	18,734	351	0.15	8.26
		41–60	20	11,096	0.18	9.76	Black	103	6,109	1.69	34.92	Female	30	14,393	245	0.21	12.24
		61–80	23	13,569	0.17	9.87	Hispanic	92	14,305	0.64	13.61						
		>80	6	2,957	0.20	10.17	Asian or Pacific Islander	100	9,179	1.09	23.75						
							American Indian/ Alaska Native	3	532	0.56	11.11						
							Unknown	1	924	0.11	7.69						

[1], lip, tongue, gum, floor of mouth, & other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle & inner ear, larynx, trachea, orbit & lacrimal gland, retina, eyeball, eye, NOS. GI, Gastrointestinal; GU, Genitourinary; GYN, Gynecologic; NOS, not otherwise specified.

Table S2 Median survival of patients with bone metastases by age, race, and gender

Site	Sub-site	Age			Race			Gender		
		Age category in years	Number of patients with bone metastases	Median survival in months (interquartile range)	Race	Number of patients with bone metastases	Median survival in months (interquartile range)	Gender	Number of patients with bone metastases	Median survival in months (interquartile range)
Head and neck	Head and neck[1]	18–40	57	15 [8–32]	White	819	8 [3–16]	Male	780	8 [3–18]
		41–60	395	9 [3–21]	Black	103	8 [3–18]	Female	334	8 [3–15]
		61–80	522	7 [3–16]	Hispanic	99	8 [3–20]			
		>80	96	4 [1–10]	Asian or Pacific Islander	80	15 [8–35]			
					American Indian/ Alaska Native	5	10 [5–15]			
					Unknown	8	11 [3–16]			
Thyroid	Thyroid	18–40	37	52 [9–NR]	White	380	21 [4–82]	Male		22 [4–82]
		41–60	186	66 [7–NR]	Black	103	27 [3–60]	Female		23 [3–NR]
		61–80	370	22 [4–NR]	Hispanic	92	21 [3–64]			
		>80	86	6 [2–23]	Asian or Pacific Islander	100	49 [9–NR]			
					American Indian/ Alaska Native	3	2 [NR]			
					Unknown	1	5 [NR]			
Breast	Breast	18–40	1,140	42 [20–72]	White	10,908	28 [8–59]	Male		23 [8–54]
		41–60	6,294	32 [13–66]	Black	2,447	20 [6–43]	Female		27 [8–57]
		61–80	7,022	25 [9–53]	Hispanic	1,707	32 [12–63]			
		>80	1,805	12 [2–32]	Asian or Pacific Islander	1,067	31 [12–62]			
					American Indian/ Alaska Native	85	34 [12–NR]			
					Unknown	47	NR [22–NR]			
Lung	Small cell	18–40	25	8 [4–10]	White	7,793	5 [1–10]	Male	5103	5 [1–10]
		41–60	2,320	7 [2–11]	Black	714	8.0 [2.0–16.0]	Female	4,120	6 [1–10]
		61–80	6,070	5 [1–10]	Hispanic	399	4 [1–10]			
		>80	808	2 [0–6]	Asian or Pacific Islander	271	6 [2–10]			
					American Indian/ Alaska Native	42	3 [1–9]			
					Unknown	4	18 [5–18]			
	Squamous cell carcinoma	18–40	32	8 [2.0–15.0]	White	5,869	3.0 [1.0–7.0]	Male	5,351	3.0 [1.0–7.0]
		41–60	1,615	4.0 [2.0–9.0]	Black	1,107	3.0 [1.0–8.0]	Female	2,516	3.0 [1.0–7.0]
		61–80	5,100	3.0 [1.0–7.0]	Hispanic	440	3.0 [1.0–9.0]			
		>80	1,120	2.0 [1.0–5.0]	Asian or Pacific Islander	402	4.0 [1.0–9.0]			
					American Indian/ Alaska Native	41	4.0 [1.0–11.0]			
					Unknown	8	2.0 [1.0–9.0]			
	Adenocarcinoma	18–40	3	14 [5–29]	White	21,226	4 [1–12]	Male	16,070	4 [1–11]
		41–60	38	6 [2–16]	Black	3,373	4 [1–11]	Female	13,776	5 [2–15]
		61–80	111	4 [1–12]	Hispanic	2,122	6 [2–15]			
		>80	32	3 [1–8]	Asian or Pacific Islander	2,961	11 [3–25]			
					American Indian/ Alaska Native	133	5 [1–10]			
					Unknown	41	13 [2–32]			
	Bronchioloalveolar adenocarcinoma	18–40	-	22 [4–38]	White	92	6 [2–16]	Male	96	7 [2–19]
		41–60	50	10 [5–21]	Black	20	5 [1–16]	Female	88	9 [3–2]
		61–80	84	7 [2–21]	Hispanic	11	11 [4–21]			
		>80	13	6 [2–12]	Asian or Pacific Islander	23	22 [9–39]			
					American Indian/ Alaska Native	1	NA			
					Unknown	0	NA			
	Non-small cell and other	18–40	30	7 [5–15]	White	3,297	3 [1–7]	Male	2,681	3 [1–7]
		41–60	1,163	4 [1–9]	Black	522	3 [1–7]	Female	1,728	3 [1–9]
		61–80	2,631	3 [1–6]	Hispanic	310	3 [1–10]			
		>80	615	2 [1–5]	Asian or Pacific Islander	291	4 [1–15]			
					American Indian/ Alaska Native	14	2 [1–5]			
					Unknown	5	2 [1–5]			
GI	Esophagus	18–40	29	9 [2–31]	White	198	11 [4–37]	Male	287	11 [4–35]
		41–60	703	13 [4–38]	Black	14	12 [5–33]	Female	1,788	11 [3–44]
		61–80	1,142	11 [4–38]	Hispanic	16	13 [4–43]			
		>80	201	11 [4–32]	Asian or Pacific Islander	9	13 [4–43]			
					American Indian/ Alaska Native	1	8 [4–19]			
					Unknown	0	NA			
	Gastric	18–40	130	5 [1–10]	White	1,114	4 [1–9]	Male	1,283	3 [1–8]
		41–60	674	4 [1–9]	Black	198	3 [1–7]	Female	664	3 [1–8]
		61–80	936	3 [1–9]	Hispanic	374	3 [1–8]			
		>80	207	2 [0–5]	Asian or Pacific Islander	239	3 [1–8]			
					American Indian/ Alaska Native	20	5 [1–6]			
					Unknown	2	NA			
	Hepatobiliary	18–40	44	7 [3–13]	White	1,816	3 [1–8]	Male	2,365	3 [1–7]
		41–60	1,104	3 [1–7]	Black	441	3 [1–7]	Female	821	3 [1–8]
		61–80	1,735	3 [1–7]	Hispanic	544	3 [1–8]			
		>80	303	2 [0–5]	Asian or Pacific Islander	345	3 [1–7]			
					American Indian/ Alaska Native	37	3 [1–9]			
					Unknown	3	5 [1–5]			
	Pancreatic	18–40	41	8 [2–20]	White	51,673	2 [1–6]	Male	1,695	2 [1–6]
		41–60	727	3 [1–8]	Black	9,028	2 [1–6]	Female	1,176	2 [1–6]
		61–80	1,691	2 [1–6]	Hispanic	7,957	2 [1–8]			
		>80	376	1 [0–3]	Asian or Pacific Islander	5,454	2 [1–6]			
					American Indian/ Alaska Native	406	1 [0–5]			
					Unknown	142	0 [0–1]			
	Colorectal	18–40	131	10 [3–23]	White	166,744	5 [1–14]	Male	1,878	5 [1–15]
		41–60	1,023	9 [3–20]	Black	30,329	4 [2–15]	Female	1,207	5 [1–14]
		61–80	1,459	4 [1–13]	Hispanic	28,276	5 [2–18]			
		>80	472	2 [0–5]	Asian or Pacific Islander	20,419	7 [2–19]			
					American Indian/ Alaska Native	1,850	6 [4–9]			
					Unknown	1,654	14 [2–14]			
	Anal	18–40	2	NA	White	9,268	10 [5–27]	Male	53	8 [4–22]
		41–60	52	14 [5–46]	Black	1,344	6 [3–22]	Female	68	14 [4–27]
		61–80	56	9 [4–24]	Hispanic	1,097	4 [2–NR]			
		>80	11	3 [1–8]	Asian or Pacific Islander	311	5 [1–8]			
					American Indian/ Alaska Native	65	NA			
					Unknown	65	NA			
	Other GI	18–40	21	4 [1–11]	White	15,935	3 [1–8]	Male	344	3 [1–10]
		41–60	237	2 [1–8]	Black	3,324	2 [0–10]	Female	512	2 [1–7]
		61–80	457	3 [1–9]	Hispanic	2,624	2 [0–6]			
		>80	141	2 [0–5]	Asian or Pacific Islander	1,379	2 [1–10]			
					American Indian/ Alaska Native	142	4 [1–6]			
					Unknown	109	2 [2–NR]			
GU	Renal	18–40	128	10 [4–24]	White	68,184	6 [2–17]	Male	3,820	6 [2–18]
		41–60	1,740	8 [3–26]	Black	12,112	5 [2–14]	Female	1,783	5 [2–15]
		61–80	2,976	6 [2–17]	Hispanic	14,206	7 [2–19]			
		>80	759	3 [1–7]	Asian or Pacific Islander	5,234	6 [2–20]			
					American Indian/ Alaska Native	885	6 [2–12]			
					Unknown	500	5 [5–50]			
	Bladder	18–40	15	8 [4–10]	White	102,014	4 [1–10]	Male	1,390	4 [1–10]
		41–60	385	5 [2–11]	Black	7,255	4 [2–8]	Female	450	3 [1–8]
		61–80	1,029	4 [1–11]	Hispanic	7,846	4 [1–6]			
		>80	411	2 [1–6]	Asian or Pacific Islander	5,196	5 [1–10]			
					American Indian/ Alaska Native	415	1 [1–5]			
					Unknown	1,553	5 (NR)			
	Prostate	18–40	14	22 [13–38]	White	234,522	25 [10–53]	Male	19,750	25 [11–55]
		41–60	3,321	34 [17–72]	Black	53,642	25 [11–55]	Female	0	NA
		61–80	11,230	29 [12–65]	Hispanic	32,440	24 [11–61]			
		>80	5,185	15 [5–33]	Asian or Pacific Islander	16,142	34 [13–NR]			
					American Indian/ Alaska Native	1,316	26 [10–55]			
					Unknown	8,782	NR			
	Testicular	18–40	87	NR [8–NR]	White	11,001	21.0 [4.5–NR]	Male	143	NR [7–NR]
		41–60	42	32 [4–NR]	Black	506	NA	Female	0	NA
		61–80	14	8 [3–NR]	Hispanic	1,959	NR [NR–NR]			
		>80	-	NA	Asian or Pacific Islander	712	NR [14.0–NR]			
					American Indian/ Alaska Native	180	14.0 [NR]			
					Unknown	303	NR			
	Other GU	18–40	6	5 [5–18]	White	6,130	4 [1–9]	Male	199	4 [1–9]
		41–60	40	7 [2–14]	Black	703	5 [3–9]	Female	68	4 [1–10]
		61–80	153	5 [1–9]	Hispanic	977	4 [1–9]			
		>80	88	2 [1–7]	Asian or Pacific Islander	549	5 [2–14]			
					American Indian/ Alaska Native	41	7 [7–9]			
					Unknown	67	4 [1–9]			
GYN	Ovarian	18–40	25	5 [2–9]	White	25,567	4 [1–15]	Male	0	NA
		41–60	121	7 [2–19]	Black	3,270	7 [2–36]	Female	422	5 [1–17]
		61–80	202	5 [1–23]	Hispanic	5,073	4 [1–10]			
		>80	74	2 [0–7]	Asian or Pacific Islander	3,209	7 [1–14]			
					American Indian/ Alaska Native	220	2 [NR–NR]			
					Unknown	129	NA			
	Endometrial	18–40	17	5 [5–10]	White	12,015	6 [2–17]	Male	0	NA
		41–60	320	8 [2–20]	Black	3,084	4 [1–12]	Female	847	6 [2–15]
		61–80	436	6 [1–15]	Hispanic	5,164	6 [1–15]			
		>80	74	3 [1–10]	Asian or Pacific Islander	2,124	9 [3–28]			
					American Indian/ Alaska Native	208	10 [9–20]			
					Unknown	179	NA			
	Cervical	18–40	75	8 [3–15]	White	120	6 [2–16]	Male	0	NA
		41–60	163	7 [3–18]	Black	1,347	5 [3–12]	Female	558	6 [2–15]
		61–80	190	5 [2–13]	Hispanic	1,522	6 [2–14]			
		>80	30	3 [1–7]	Asian or Pacific Islander	751	12 [4–23]			
					American Indian/ Alaska Native	104	1 [NR–13]			
					Unknown	112	NR [NR–NR]			
	Other GYN	18–40	7	8 [3–NR]	White	24,834	5 [2–17]	Male	0	NA
		41–60	49	9 [3–29]	Black	2,054	3 [2–16]	Female	179	6 [2–16]
		61–80	97	4 [2–12]	Hispanic	4,109	4 [2–16]			
		>80	26	3 [1–16]	Asian or Pacific Islander	1,858	9 [6–14]			
					American Indian/ Alaska Native	144	1 [1–1]			
					Unknown	128	1 [1–1]			
Brain and other nervous system	Brain and other nervous system	18–40	10	NR [15–NR]	White	57,307	10 [3–NR]	Male	29	15 [3–NR]
		41–60	20	NR [3–NR]	Black	6,109	19 [1–NR]	Female	30	19 [2–NR]
		61–80	23	8 [2–NR]	Hispanic	14,305	NR [2–NR]			
		>80	6	NR [NR–2]	Asian or Pacific Islander	9,179	1 [NR]			
					American Indian/ Alaska Native	532	NA			
					Unknown	924	NA			

[1], lip, tongue, gum, floor of mouth, & other mouth, salivary gland, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavity (including nasal cartilage), accessory, sinuses, middle & inner ear, larynx, trachea, orbit & lacrimal gland, retina, eyeball, eye, NOS. GI, gastrointestinal; GU, genitourinary; GYN, gynecologic; SCLC, small-cell lung cancer; NSCLC (NOS/others), non-small cell lung cancer not otherwise specified or non-small cell lung cancer other lung cancer; ADC, adenocarcinoma of the lung; SCC, squamous cell carcinoma of the lung, NSCLC (BAC), bronchioloalveolar carcinoma; NR, not reached; NA, not applicable.