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Survival after bone metastasis by primary cancer type: a Danish population-based cohort study

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Abstract

Objective: To examine survival after bone metastases (BM) diagnosis in cancer patients by primary cancer type, and compare survival amongst patients with bone metastases only or with additional synchronous metastases.

Methods: We included all patients aged 18 years and older with incident hospital diagnosis of solid cancer between 1994 -2010, subsequently diagnosed with BM until 2012, from the Danish National Patient Registry, to this prospective cohort study. We followed patients from date of diagnosis of BM until death, emigration, or December 31st 2012, whichever came first. We computed 1, 3 and 5-year survival (%) and the corresponding 95% confidence intervals (CI) stratified on primary cancer type. Comparing patients with BM only and patients with other synchronous metastases, we estimated crude and adjusted Hazard Ratios (HR) and corresponding 95% CI for mortality.

Results: We included 17,251 patients with BM. Most common primary cancer types were prostate (34%), breast (22%) and lung (20%). One-year survival after diagnosis of BM was lowest in lung cancer patients (10%, 95% confidence interval (CI) 9-11) and highest in patients with breast cancer (51%, 50-53). At 5-years of follow-up only patients with breast cancer had over 10% survival (13%, 11-14). The risk of mortality was increased for the majority of cancer types among patients with bone and synchronous metastases compared with bone only (adjusted relative risk 1.29 – 1.57), except for cervix, ovarian and bladder cancer.

Conclusions: While patients with bone metastases after most primary cancers have poor survival, one of ten patients with BM from breast cancer survived 5-years.

Strengths and limitations of this study:

- Strengths of this study include its large size and population-based design
- The high-quality Danish medical databases provide complete hospital contact and follow-up of all patients, thereby limiting the risk of referral and diagnostic bias
- Although the coding is reasonable accurate, the proportions of patients with bone metastases are likely to be underestimated
- We used the date of hospital diagnosis of bone metastases as registered in the DNPR, this date may not be the same as the first evidence of metastasis
- We only included synchronous metastases diagnosed prior to the bone metastasis, thus the figure of 90% with bone metastases only, reflects that bone was the first location of metastases.

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Competing interest statement: The authors report no conflict of interest.

Introduction

Bone is the third most common site of metastatic disease in cancer patients [1;2]. Bone metastases occur in every cancer type, but are most common in patients with cancers of the breast, prostate or lung [2-4]. Such metastases are often painful and can cause considerable morbidity [2;4;5], including a range of skeletal related events [6], and is associated with substantial use of hospital resources [7;8].

Population-based reports on length of survival after bone metastases from many primary cancer types are lacking. In patients with breast, prostate and renal cancer, the reported median survival range from 17- 33 months for patients with bone metastases [9-13], and survival increases with longer time between primary diagnosis and such metastases [14]. On the other hand, survival is low for patients with primary lung cancer and bone metastases (one year survival: 12.1% (95% CI: 10.0–14.3%)[15].

Previous research has suggested that survival among patients with bone metastases is associated with tumour and other disease characteristics. In a clinical setting, having other synchronous metastases in addition to bone metastases was associated with impaired prognosis compared to bone metastasis only in patients with primary gynaecological or prostate cancer [11;16]. For other cancer types this information is not available in a population-based setting. We hypothesize that survival for other cancers will follow the above mentioned pattern, being better when no synchronous metastases are observed.

Thus, the aim of this study was to estimate survival after bone metastases in cancer patients by primary cancer type, and to compare mortality amongst patients with bone metastases only with mortality of patients who were diagnosed with additional other synchronous metastases.

Material and methods

Study population

We conducted this population based cohort study in Denmark, with about 5.6 million inhabitants, based on a linkage of prospectively collected data from Danish medical registries. Denmark is a welfare state with tax-funded universal access to health care, providing primary and secondary care without out-of-pocket expenses and partial reimbursement for most prescribed medications. Individual-level data from all Danish registries can be linked via the unique personal identifier, the CPR number, assigned at birth, registered in the Danish Civil Registration system [17].

Cancer patients with bone metastasis

We included all adult (over 18 years of age) residents of Denmark diagnosed with cancer in the Danish Cancer Registry from January 1st 1994 to December 31st 2010, and with a diagnosis of bone metastasis registered in the Danish National Patient Registry (DNPR) on or after the date of primary cancer diagnosis until December 31st 2012 [18]. DNRP holds discharge diagnoses from all inpatient admissions to Danish hospitals since 1977 and hospital outpatient clinic diagnoses since 1995. For each visit, the DNPR includes information on admission and discharge, procedures and up to 20 diagnoses. Since 1994, the diagnostic information has been coded according to the International classification of diseases, 10th Revision. All diagnostic codes are given in appendix 1.

We defined patients having other metastases prior to or at diagnosis of bone metastases as patients with bone plus synchronous metastases.

Covariates

From the DNPR, we collected information on the 19 major non-psychiatric comorbidities in the Charlson Comorbidity Index (CCI) prior to diagnosis of bone metastases [19], using a modified version where any tumor, leukemia, lymphoma og metastatic solid tumor is excluded in the calculation. Based on the CCI score, we defined three comorbidity levels: low (score of 0), medium (score of 1-2), and high (score of 3+).

Follow-up

Patients were followed from diagnosis of bone metastasis to date of death, emigration, or December 31st 2012, whichever came first. Information on vital status (alive, dead, emigration) was obtained from the Danish Civil Registration System (CRS) [17]. The CRS contains electronic records of age, gender, vital status and place of residence (address) for the entire Danish population since 1968, and is updated daily.

This study was approved by the Danish Data Protection Agency (Record Nr. 1-16-02-1-08). As this registry-based study did not involve patient contact, no separate permission from the Danish Scientific Ethics Committee was required, according to Danish legislation.

Statistical analysis

We examined the ten most common primary cancer types, and for the breast, prostate and lung primary cancer types, we investigated the distribution of bone metastases over time by primary cancer. We calculated the median age at bone metastasis diagnosis and median time from cancer diagnosis to bone metastasis for each cancer type, separately for males and females. We calculated the percentage of patients with bone metastases only (no other metastases), compared to bone plus other synchronous metastases at time of bone metastasis diagnosis. We computed 1-, 3- and 5-year survival with corresponding 95% confidence

intervals (CI) using the Kaplan-Meier methods, overall, and stratified on patients with bone metastasis only versus those with bone metastasis and other metastasis, starting at time of bone metastasis. By Cox regression, we estimated hazard ratios for death and the corresponding 95% confidence interval (CI) separately for each primary cancer type, comparing bone metastases only with bone and additional metastases. The proportional hazard assumption was fulfilled. The HR was adjusted for age, gender, CCI score, and period of diagnosis.

We used SAS statistical software, version 9.2 (SAS Institute, Cary, NC), for all statistical analyses.

Results

We identified 17,251 patients with an ICD-10 code of bone metastases in Denmark among primary cancers diagnosed between 1994 and 2010, followed up for bone metastases until the end of 2012. Prostate, breast and lung cancer were the most frequent primary cancer types, accounting for 34%, 22%, and 20% of patients with bone metastases, respectively. In table 1, the distribution of bone metastasis by cancers of the lung, prostate and breast are given over time. For all these cancer types, the proportion developing bone metastasis is rather stable over time, taken into account a shorter follow-up for the last time period under investigation. Median time from primary cancer diagnoses ranged from a few months (e.g. lung cancer, 0.1 years), to several years (e.g. breast cancer, about 2.5 years) (Table 2), and were comparable between genders.

Survival

Survival after diagnosis of bone metastases varied widely by cancer type (Table 3). One-year survival after bone metastasis was lowest in lung cancer patients (10%, 95% confidence interval (CI) 9-11) and highest in patients with breast cancer (51%, 95% CI 50-53). Three-year survival ranged from 2% for lung cancer (95% CI 1-2), 12 % (96% CI 11-13) for prostate, and 25% (95% CI 23-26%) for breast cancer. At 5-years of follow-up only patients with breast cancer among the solid tumours had over 10% survival (13%, 95%CI 11-14).

Survival with and without other synchronous metastases

For all patients with bone metastasis, except malignant melanoma, around 90% of patients had only such metastasis (Table 4). Survival curves for bone metastasis after specific primary cancers, with and without presence of other metastases, are presented in figure 1. Table 4 shows the Cox regression comparing mortality for patients with and without additional metastases at time of bone metastasis diagnosis. The crude risk for mortality is increased for patients with synchronous metastasis compared with bone metastases only, except for ovary, cervix and bladder cancer, with crude HR ranging from 1.3 (95% CI 1.0-1.6) for malignant melanoma to HR= 1.6 (95% CI 1.4-1.8) for prostate cancer (Table 3) and did not change considerably when adjusted for age, gender, comorbidity and year of diagnosis.

Discussion

In this large heterogeneous cohort of 17,251 patients with bone metastases in eight overall categories, comprising ten specific primary cancer types, we find that the prognosis after diagnosis of bone metastasis is depending on primary cancer type. Furthermore, the prognosis is poorer when other metastases are present at time of bone metastasis diagnosis.

Strengths of this study include its large size and population-based design, made possible through access to high-quality Danish medical databases providing a complete hospital contact and follow-up of all patients, thereby limiting the risk of referral and diagnostic bias. Our data derive from a wide range of unselected patients in real life and may be transferrable to other population-based settings.

Our registry-based population approach also introduces some limitations. The validity of our findings depends on the completeness and the accuracy of reporting to the DNPR. The diagnoses registered in the DNPR as compared with a review of medical records have a high specificity, but the completeness was low, primary related to metastases without symptoms [20]. Thus, although the coding is reasonable accurate, the proportions of patients with bone metastases are likely to be underestimated [20]. It is possible that in lieu of other metastases, such as lung metastases, additional bone metastases would to a lesser extent be recorded, this non-random misclassification would possibly influence the estimates, resulting in an even more increased risk of mortality among patients with additional metastases compared with bone only. On the other hand, if patients with other synchronous metastases not have their bone metastases recorded, they would not be included in the study, and therefore lead to selection bias, and possibly a lower mortality among the included patients. We only included synchronous metastases diagnosed prior to the bone metastasis, thus the figure of 90% with bone metastases only, reflects that bone was the first location of metastases. Furthermore, we did not take into account the patients who developed a second primary cancer, which again might experience poorer survival. We here assumed that the bone metastasis arose from the first cancer. Finally, we used the date of hospital diagnosis of bone metastases as registered in the DNPR, and thus, the date may not be the same as the first evidence of metastasis, which may also explain why median survival is shorter than reported by others.

This study corroborates previous research findings regarding prognosis after bone metastases [10-12]. As noted by Ibrahim et al, most bone metastases are secondary to breast, prostate, and lung cancer [5]. Generally, the 1-year survival rates observed in the present study are lower than other clinical based studies [11;12]. For example, Drzymalski et al estimated a one year survival of 73% based on a study on patients in the Prostate Clinical Research Information System at the Dana-Farber Cancer Institute [11]. It is possible that in countries having high levels of screening for prostate cancer, the bone metastases may be detected earlier via elevated PSA screening, and therefore have a better prognosis. Nonetheless, most reports come from specialized cancer treatment facilities, thus conceivably encompass selected groups of patients and accordingly suffer from bias when compared to results of population-based studies applied to the real life situation.

In accordance with our hypothesis, and previous findings [11;16], having other metastases impaired prognosis after bone metastasis diagnosis. Additional metastases might be indicative of a more aggressive primary tumour. However, since the patients with other synchronous metastases, in addition to bone, may have had their other metastasis for some time, it is not surprising that their mortality is higher, simply because a longer time had elapsed after the primary diagnosis. Nonetheless, as time from diagnosis of primary cancer to bone metastasis can be regarded as an intermediate variable, we have not controlled for this in an adjusted analysis.

Unfortunately, we did not have individual-level information about the primary treatments and the specific bone targeted therapy eventually the patients received. We investigate a long time

course, and thus the observed prognosis can be influenced by treatments implemented during the study period. Further studies are warranted to examine the response to the bone targeted therapy for the different cancer types. Furthermore, a detailed examination the natural history of the patients with bone metastasis, including a detailed description of skeletal related events, is beyond the scope of this article, but also warrants further examination.

In conclusion, this population-based registry study with complete follow-up shows that there is a significant proportion of patients with long-term survival with bone metastases in selected malignant diseases, such as breast cancer.

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Author contributions:

CFC and HTS conceived the idea for the study, and developed the study concept and design together with ES, and SPU performed the statistical analysis. All authors (ES, CFC, SPU, MR, HTS) made substantial contributions to the interpretation of the data. ES, CFC and HTS drafted the manuscript, and all authors (ES, CFC, SPU, MR, HTS) revised it critically for important intellectual content. All authors (ES, CFC, SPU, MR, HTS) approved its final version, and agreed to be accountable for all aspects of the work.

Data sharing statement: No additional data are available.

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Figure legend:

Figure 1.Cumulative survival comparing bone metastases only with bone metastases and other synchronous metastases

Table 1. Patients who develop bone metastasis by all breast, lung and prostate cancers over time

Cancer type	Year of cancer diagnosis	Patients who develop bone metastasis (n)	Patients with cancer type (n)	Proportion developing bone metastasis (%)
Lung	1994-1997	445	13,713	3
	1998-2001	633	14,419	4
	2002-2006	1,188	19,504	6
	2007-2010	1,137	17,270	7
Breast	1994-1997	936	13,623	7
	1998-2001	1,001	15,145	7
	2002-2006	1,223	20,348	6
	2007-2010	629	19,893	3
prostate	1994-1997	1,034	6,041	17
	1998-2001	1,602	7,774	21
	2002-2006	2,181	13,588	16
	2007-2010	1,124	15,454	7

Table 2. Median age (years) at bone metastasis diagnosis, and median time (days) since primary cancer to bone metastases by primary cancer type

	Males			Females		
	N	Median age at diagnosis, years (IQR) (years)	Median time from primary cancer diagnosis to BM, (IQR) (days)	N	Median age at diagnosis (years)	Median time from primary cancer diagnosis to BM, (IQR) (days)
Digestive organs	876	67 (60-75)	296 (35-926)	554	66 (58-75)	357 (57-963)
Colon (incl rectosig.)	265	69 (62-77)	402 (54-1,118)	234	66 (58-75)	403 (63-1,051)
Rectum	256	69 (62-76)	768 (303-1,387)	144	66 (57-76)	673 (296-1,358)
Respiratory organs	2,040	67 (60-73)	37 (14-197)	1,459	65 (59-73)	43 (14-228)
Lung	1,961	67 (60-73)	35 (14-185)	1,442	65 (59-73)	42 (14-221)
Malignant Melanoma	148	62 (51-73)	698 (268-1,404)	121	63 (50-73)	570 (177-1,749)

Breast	18	71 (53-79)	854 (37-1,515)	3,771	64 (55-72)	918 (160-1,812)
Female genital organs				288	65 (54-75)	590 (214-1,374)
Cervix				74	53 (45-67)	602 (288-1,230)
Ovary				65	61 (51-68)	566 (243-1,180)
Male genital organs	5,971	74 (67-80)	484 (60-1,110)			
Prostate	5,941	74 (68-80)	485 (61-1,112)			
Urinary organs	994	68 (60-75)	220 (29-668)	458	70 (61-77)	123 (22-567)
Kidney	502	64 (57-72)	59 (15-483)	293	68 (60-76)	59 (12-437)
Bladder	423	71 (63-77)	376 (139-849)	123	72 (64-77)	293 (99-732)

Table 3. One-, three-, and five-year survival estimates with 95% confidence interval (CI) after bone metastasis diagnosis by primary cancer type

	1-Year survival (95% CI)	3-Year survival (95% CI)	5-Year survival (95% CI)
Digestive organs			
Colon*	21 (18 - 25)	7 (5- 10)	3 (2 - 5)
Rectum	22 (18 - 26)	3 (2- 5)	2 (1 - 3)
Respiratory organs			
Lung	10 (9- 11)	2 (1- 2)	1 (0.5 - 1)
Malignant Melanoma	17 (12 - 22)	6 (4-10)	5 (3 - 8)
Breast	51 (50 - 53)	25 (23- 26)	13 (11 - 14)
Female genital organs			
Cervix	18 (11-28)	6 (2-14)	2 (0-7)
Ovary	33 (21-44)	15 (7-25)	8 (3-18)
Male genital organs			
Prostate	35 (34 - 37)	12 (11 - 13)	6 (5- 7)
Urinary organs			

Kidney	29	10	5
	(26- 33)	(8 - 12)	(4 - 7)
Bladder	13	5	3
	(11 - 17)	(3 - 7)	(1 - 5)

* including colonrectosigmoid

Table 4. Hazard ratios (HR), and corresponding 95% confidence intervals for mortality after bone metastases, comparing patients with and without synchronous metastases

Primary cancer		N (%)	HR (95% CI)	Adjusted* HR (95%CI)
Colon cancer	Bone metastasis only	452 (91)	1.0	1.0
	Bone + other synchronous metastases	47 (9)	1.38 (1.02 - 1.87)	1.48 (1.09 - 2.03)
Rectum cancer	Bone metastasis only	361 (90)	1.0	1.0
	Bone + other synchronous metastases	39 (10)	1.47 (1.06 - 2.05)	1.44 (1.03 - 2.03)
Lung cancer	Bone metastasis only	2,871 (84)	1.0	1.0
	Bone + other synchronous metastases	532 (16)	1.20 (1.10 - 1.32)	1.27(1.16 - 1.40)
Malignant melanoma	Bone metastasis only	172 (64)	1.0	1.0
	Bone + other synchronous metastases	97 (36)	1.26 (0.97 - 1.63)	1.29 (0.99 - 1.69)
Breast cancer	Bone metastasis only	3,268 (86)	1.0	1.0
	Bone + other synchronous metastases	521 (14)	1.42 (1.28 - 1.57)	1.47 (1.33 - 1.63)
Cervix cancer	Bone metastasis only	67 (91)	1.0	1.0
	Bone + other synchronous metastases	7 (9)	1.06 (0.48 - 2.33)	1.00(0.42 - 2.38)

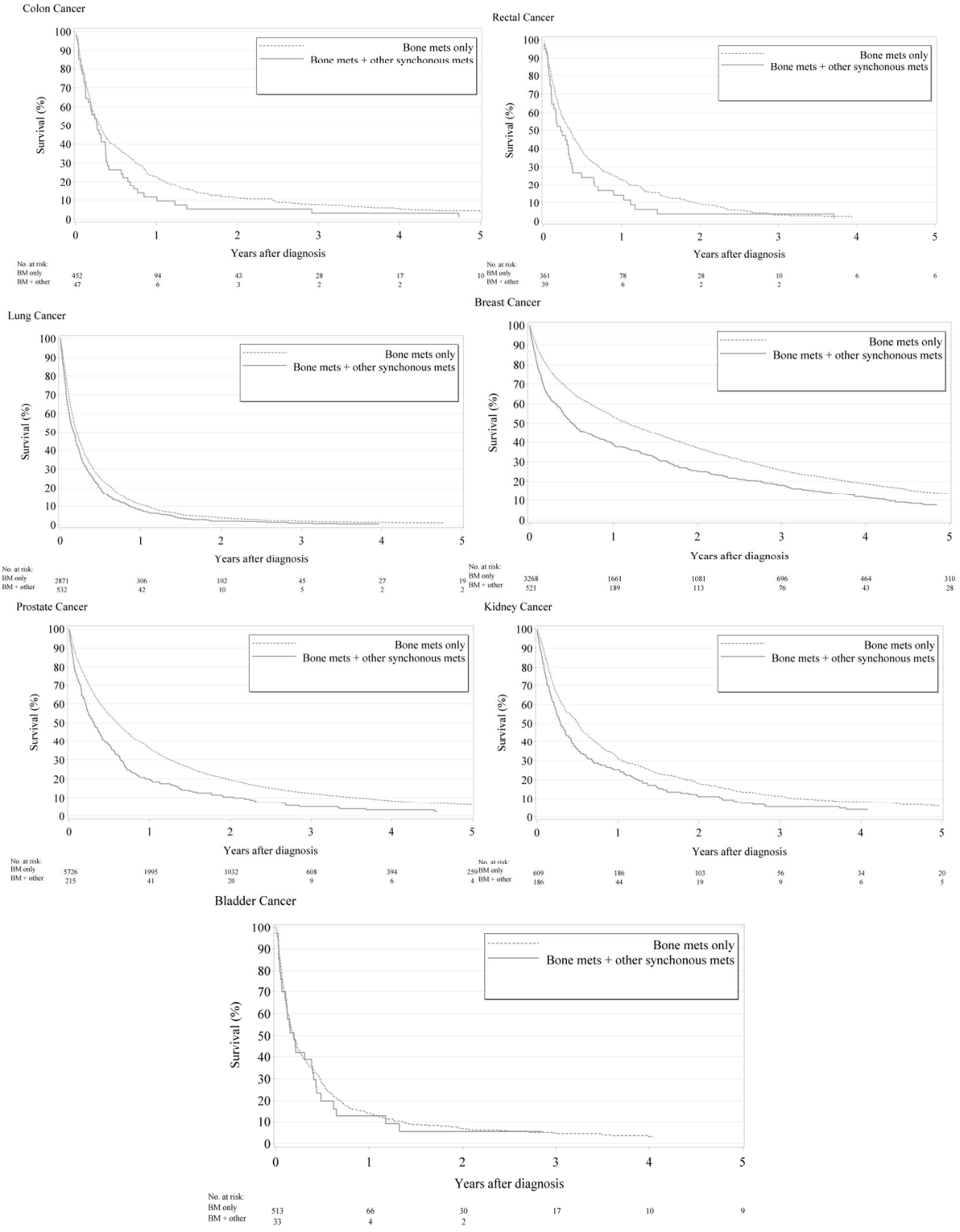
Primary cancer		N (%)	HR (95% CI)	Adjusted* HR (95%CI)
Ovarian cancer	Bone metastasis only	54 (83)	1.0	1.0
	Bone + other synchronous metastases	11 (17)	1.12 (0.56 - 2.23)	1.08 (0.51 - 2.29)
Prostate cancer	Bone metastasis only	5,726 (96)	1.0	1.0
	Bone + other synchronous metastases	215 (4)	1.55 (1.35 - 1.78)	1.57 (1.36 - 1.80)
Kidney cancer	Bone metastasis only	609 (77)	1.0	1.0
	Bone + other synchronous metastases	186 (23)	1.33 (1.12 - 1.58)	1.41 (1.18 - 1.69)
Urinary bladder cancer	Bone metastasis only	513 (94)	1.0	1.0
	Bone + other synchronous metastases	33 (6)	1.14 (0.79 - 1.65)	1.22 (0.84 - 1.77)

* Adjusted by gender, age, Charlson Comorbidity Index Score, and period of diagnosis

Appendix 1: International classification of diseases (ICD-10) codes used in the current study

	ICD-10
Bone metastases	C79.5
Any tumor	C00-C79
Other metastases present	C79.0-C79.9
Charlson Comorbidity Index conditions:	
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	K22.1; K25-K28
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0

Diabetes, Type 1	E10.0, E10.1; E10.9
Diabetes, Type 2	E11.0; E11.1; E11.9
Hemiplegia	G81; G82
Moderate to severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end-organ damage,	
Type 1	E10.2-E10.8
Type 2	E11.2-E11.8
Any tumor	C00-C75
Leukemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	C76-C80
AIDS	B21-B24



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	We hypothesize that survival for other cancers will follow the above mentioned pattern, being better when no synchronous metastases are observed.
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment	*6*	

measurement		(measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	5-6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a.
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Referred to
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 + tables
		(*b*) Report category boundaries when continuous variables were categorized	8 + tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Survival after bone metastasis by primary cancer type: a Danish population-based cohort study

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Survival after bone metastasis by primary cancer type: a Danish population-based cohort study

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Abstract

Objective: In the ten most common primary types with bone metastases, we aimed to examine survival, further stratifying on bone metastases only or with additional synchronous metastases.

Methods: We included all patients aged 18 years and older with incident hospital diagnosis of solid cancer between 1994-2010, subsequently diagnosed with BM until 2012. We followed patients from date of bone metastasis diagnosis until death, emigration, or December 31 2012, whichever came first. We computed 1, 3 and 5-year survival (%) and the corresponding 95% confidence intervals (CI) stratified on primary cancer type. Comparing patients with bone metastasis only and patients with other synchronous metastases, we estimated crude and adjusted Hazard Ratios (HR) and corresponding 95% CI for mortality.

Results: We included 17,251 patients with bone metastasis. The most common primary cancer types with bone metastasis were prostate (34%), breast (22%) and lung (20%). One-year survival after bone metastasis diagnosis was lowest in lung cancer patients (10%, 95% confidence interval (CI) 9-11) and highest in patients with breast cancer (51%, 50-53). At 5-years of follow-up only patients with breast cancer had over 10% survival (13%, 11-14). The risk of mortality was increased for the majority of cancer types among patients with bone and synchronous metastases compared with bone only (adjusted relative risk 1.29 – 1.57), except for cervix, ovarian and bladder cancer.

Conclusions: While patients with bone metastases after most primary cancers have poor survival, one of ten patients with bone metastasis from breast cancer survived 5-years.

Strengths and limitations of this study:

- Strengths of this study include its large size and population-based design
- The high-quality Danish medical databases provide complete hospital contact and follow-up of all patients, thereby limiting the risk of referral and diagnostic bias
- Although the coding is reasonable accurate, the proportions of patients with bone metastases are likely to be underestimated
- We used the date of hospital diagnosis of bone metastases as registered in the DNPR, this date may not be the same as the first evidence of metastasis
- We only included synchronous metastases diagnosed prior to the bone metastasis, thus the figure of 90% of patients having bone metastases only, reflects that bone was the first location of metastases.

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Competing interest statement: The authors report no conflict of interest.

Introduction

Bone is the third most common site of metastatic disease in cancer patients [1;2]. Bone metastases occur in every cancer type, but are most common in patients with cancers of the breast, prostate or lung [2-4]. Such metastases are often painful and can cause considerable morbidity [2;4;5], including a range of skeletal related events [6], and is associated with substantial use of hospital resources [7;8].

Population-based reports on length of survival after bone metastases from many primary cancer types are lacking. In patients with breast, prostate and renal cancer, the reported median survival ranges from 12-33 months for patients with bone metastases [9-14], and survival increases with longer time between primary diagnosis and such metastases [15]. On the other hand, survival is low for patients with primary lung cancer and bone metastases, one year survival ranging from 9.5-12% [16;17].

Previous research has suggested that survival among patients with bone metastases is associated with tumour and other disease characteristics. In a clinical setting, having other synchronous metastases in addition to bone metastasis was associated with impaired prognosis compared to bone metastasis only in patients with primary gynaecological or prostate cancer [11;18]. For other cancer types this information is not available in a population-based setting. We hypothesize that survival for other cancers will follow the above mentioned pattern, being better when no synchronous metastases are observed.

Thus, in the ten most common solid cancers with bone metastasis, we aimed to estimate survival, and to compare mortality amongst patients with bone metastasis only with mortality of patients who were diagnosed with additional other synchronous metastases.

Material and methods

Study population

We conducted this population based cohort study in Denmark, with about 5.6 million inhabitants, based on a linkage of prospectively collected data from Danish medical registries. Denmark is a welfare state with tax-funded universal access to health care, providing primary and secondary care without out-of-pocket expenses and partial reimbursement for most prescribed medications. Individual-level data from all Danish registries can be linked via the unique personal identifier, the CPR number, assigned at birth, registered in the Danish Civil Registration system [19].

Cancer patients with bone metastasis

We included all adult (over 18 years of age) residents of Denmark diagnosed with cancer in the Danish Cancer Registry from January 1st 1994 to December 31st 2010, and with a diagnosis of bone metastasis registered in the Danish National Patient Registry (DNPR) on or after the date of primary cancer diagnosis until December 31st 2012 [20]. DNRP holds discharge diagnoses from all inpatient admissions to Danish hospitals since 1977 and hospital outpatient clinic diagnoses since 1995. For each visit, the DNPR includes information on admission and discharge, procedures and up to 20 diagnoses. Since 1994, the diagnostic information has been coded according to the International classification of diseases, 10th Revision. All diagnostic codes are given in the appendix.

We stratified patients with bone metastasis to bone metastasis at time of primary cancer diagnosis or more than 3 months after primary cancer diagnosis. Bone metastasis diagnosed more than 3 months after cancer diagnosis were further stratified into bone metastasis only

(no other metastasis) or bone with other synchronous metastases, defined as patients having other metastases prior to diagnosis of bone metastases.

Covariates

From the DNPR, we collected information on the 19 major non-psychiatric comorbidities in the Charlson Comorbidity Index (CCI) prior to diagnosis of bone metastasis [21], using a modified version where any tumor, leukemia, lymphoma andmetastatic solid tumor is excluded in the calculation. Based on the CCI score, we defined three comorbidity levels: low (score of 0), medium (score of 1-2), and high (score of 3+).

Follow-up

Patients were followed from diagnosis of bone metastasis to date of death, emigration, or December 31st 2012, whichever came first. Information on vital status (alive, dead, emigration) was obtained from the Danish Civil Registration System (CRS) [19]. The CRS contains electronic records of age, gender, vital status and place of residence (address) for the entire Danish population since 1968, and is updated daily.

This study was approved by the Danish Data Protection Agency (Record Nr. 1-16-02-1-08). As this registry-based study did not involve patient contact, no separate permission from the Danish Scientific Ethics Committee was required, according to Danish legislation.

Statistical analysis

We examined the ten most common primary cancer types with bone metastases. For the three most common types: breast, prostate and lung we investigated the distribution of bone metastases, stratified on bone metastasis presence at time of primary cancer diagnosis or more

than 3 months after diagnosis. We computed 1-, 3- and 5-year survival with corresponding 95% confidence intervals (CI) using the Kaplan-Meier methods for all bone metastasis after all cancer types.

We further stratified on bone metastases only and bone plus other synchronous metastases, restricted to patients diagnosed with bone metastases more than 3 months after primary cancer diagnosis. We calculated the median age at bone metastasis diagnosis and median time from cancer diagnosis to bone metastasis for each cancer type, and computed Kaplan-Meier survival curves for this stratification. We calculated the percentage of patients with bone metastases only, compared to bone plus other synchronous metastases at time of bone metastasis diagnosis. By Cox regression, we estimated hazard ratios for death and the corresponding 95% confidence interval (CI) separately for each primary cancer type, comparing bone metastases only with bone and additional metastases. The proportional hazard assumption was fulfilled. The HR was adjusted for age, gender, CCI score, and period of diagnosis.

We used SAS statistical software, version 9.2 (SAS Institute, Cary, NC), for all statistical analyses.

Results

In the ten most common primary cancers with bone metastasis, we identified 17,251 patients diagnosed between 1994 and 2010, followed up for bone metastasis until the end of 2012. Prostate, breast and lung cancer were the most frequent primary cancer types, accounting for 34%, 22%, and 20% of patients with bone metastasis, respectively. In table 1, the distribution of bone metastasis by cancers of the lung, prostate and breast are given over time. For breast

and prostate cancer, the proportion developing bone metastasis is rather stable over time, taken into account a shorter follow-up for the last time period under investigation. However, for lung cancer there seems to be a slight increase in proportion over time.

Survival

Survival after diagnosis of bone metastasis (all) varied widely by cancer type (Table 2). One-year survival after bone metastasis was lowest in lung cancer patients (10%, 95% confidence interval (CI) 9-11) and highest in patients with breast cancer (51%, 95% CI 50-53). Three-year survival ranged from 2% for lung cancer (95% CI 1-2), 12 % (96% CI 11-13) for prostate, and 25% (95% CI 23-26%) for breast cancer. At 5-years of follow-up only patients with breast cancer among the solid tumours had over 10% survival (13%, 95%CI 11-14).

Bone metastasis only versus bone metastasis with other synchronous metastases

Median time from primary cancer diagnoses to bone metastasis, restricted to patients without bone metastasis within 3 months of being diagnosed with the primary cancer ranged from close to one year (e.g. lung cancer, 279-295 days), to several years (e.g. breast cancer, about 3.5-4 years) (Table 3). Median time to bone metastasis was comparable for bone metastasis only and bone metastasis with synchronous metastasis.

For all patients with bone metastasis, except malignant melanoma, around 90% of patients had only such metastasis (Table 4). Survival curves for bone metastasis after specific primary cancers, with and without presence of other metastases, are presented in figure 1. Table 4 shows the Cox regression comparing mortality for patients with and without additional metastases at time of bone metastasis diagnosis. The crude risk for mortality is increased for patients with synchronous metastasis compared with bone metastasis only, except for ovary,

cervix and bladder cancer, with crude HR ranging from 1.3 (95% CI 1.0-1.6) for malignant melanoma to HR= 1.6 (95% CI 1.4-1.8) for prostate cancer (Table 4) and did not change considerably when adjusted for age, gender, comorbidity and year of diagnosis.

Discussion

In this large heterogeneous cohort of 17,251 patients with bone metastasis in the ten specific primary cancer types where bone metastases are most commonly observed, we find that the prognosis after diagnosis of bone metastasis is depending on primary cancer type. Furthermore, the prognosis is poorer when other metastases are present at time of bone metastasis diagnosis.

Strengths of this study include its large size and population-based design, made possible through access to high-quality Danish medical databases providing a complete hospital contact and follow-up of all patients, thereby limiting the risk of referral and diagnostic bias. Our data derive from a wide range of unselected patients in real life and the generalizability may be transferrable to other population-based settings.

Our registry-based population approach also introduces some limitations. The validity of our findings depends on the completeness and the accuracy of reporting to the DNPR. The diagnoses registered in the DNPR as compared with a review of medical records have a high specificity, but the completeness was low, primary related to metastases without symptoms [22]. Thus, although the coding is reasonable accurate, the proportions of patients with bone metastases are likely to be underestimated [22]. It is possible that in lieu of other metastases, such as lung metastases, additional bone metastasis would to a lesser extent be recorded, this non-random misclassification would possibly influence the estimates, resulting in an even

more increased risk of mortality among patients with additional metastases compared with bone only. On the other hand, if patients with other synchronous metastases do not have their bone metastasis recorded, they would not be included in the study, and therefore lead to selection bias, and possibly a lower mortality among the included patients. We only included synchronous metastases diagnosed prior to the bone metastasis, thus the figure of 90% of patients having bone metastasis only, reflects that bone metastasis were located first, and that the patients may have developed other subsequent metastases not included in our analyses. Furthermore, we did not take into account the patients who developed a second primary cancer, which again might experience poorer survival. We here assumed that the bone metastasis arose from the first cancer. Finally, we used the date of hospital diagnosis of bone metastasis as registered in the DNPR, and thus, the date may not be the same as the first evidence of metastasis, which may also explain why median survival is shorter than reported by others.

This study corroborates previous research findings regarding prognosis after bone metastasis [10-12]. As noted by Ibrahim et al, most bone metastasis are secondary to breast, prostate, and lung cancer [5]. Generally, the 1-year survival rates observed in the present study are lower than other clinical based studies [11;12]. For example, Drzymalski et al estimated a one year survival of 73% based on a study on patients in the Prostate Clinical Research Information System at the Dana-Farber Cancer Institute [11]. It is possible that in countries with high levels of screening for prostate cancer, the bone metastasis may be detected earlier via elevated PSA screening, or with a higher proportion of castration naïve prostate cancers, and therefore have a better prognosis than observed here. For breast cancer, patients with hormone receptor positive cancers can have a long survival even with bone metastasis. However, receptor status is not known in this study. Nonetheless, most other reports come from

specialized cancer treatment facilities, thus conceivably encompass selected groups of patients and accordingly suffer from bias when compared to results of population-based studies applied to the real life situation.

In accordance with our hypothesis, and previous findings [11;18], having other metastases impaired prognosis after bone metastasis diagnosis. Additional metastases might be indicative of a more aggressive primary tumour. However, since the patients with other synchronous metastases, in addition to bone, may have had their other metastasis for some time, it is not surprising that their mortality is higher, simply because a longer time had elapsed after the primary diagnosis. Nonetheless, as time from diagnosis of primary cancer to bone metastasis can be regarded as an intermediate variable, we have not controlled for this in an adjusted analysis.

Unfortunately, we did not have individual-level information about the primary treatments and the specific bone targeted therapy eventually received by the patients. We investigated a long time course, and thus new treatments implemented during the study period can confound the observed prognosis. Further studies are warranted on incidence and survival of patients with bone metastasis over time with respect to the bone targeted therapy for the different cancer types, to examine the influence clinical options may have on prognosis. Furthermore, a detailed examination the natural history of the patients with bone metastasis, including a detailed description of skeletal related events, is beyond the scope of this article, but also warrants further examination. Another area warranting further investigation is whether the outcome differs for the different solid primary tumours according to osteolytic versus osteoblastic bone metastases. Nonetheless, as this is a population-based study covering all of Denmark, the generalizability of the study applies

In conclusion, this population-based registry study with complete follow-up shows that there is a significant proportion of patients with long-term survival with bone metastasis in selected malignant diseases, such as breast cancer.

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Author contributions:

CFC and HTS conceived the idea for the study, and developed the study concept and design together with ES, and SPU performed the statistical analysis. All authors (ES, CFC, SPU, MR, HTS) made substantial contributions to the interpretation of the data. ES, CFC and HTS drafted the manuscript, and all authors (ES, CFC, SPU, MR, HTS) revised it critically for important intellectual content. All authors (ES, CFC, SPU, MR, HTS) approved its final version, and agreed to be accountable for all aspects of the work.

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Figure legend:

Figure 1.Cumulative survival comparing bone metastasis only with bone metastasis and other synchronous metastases

Table 1. Patients who develop bone metastasis by all breast, lung and prostate cancers over time, overall and stratified into bone metastasis at time of primary cancer diagnosis or more than 3 months after primary diagnosis

Cancer type	Year of cancer diagnosis	Total number patients with cancer	Patients who develop bone metastasis					
			Total		At primary cancer diagnosis		More than 3 months after primary diagnosis	
		n	n	%	n	%	n	%
Lung	1994-1997	13,713	445	3	291	2	154	1
	1998-2001	14,419	633	4	333	2	300	2
	2002-2006	19,504	1,188	6	755	4	433	2
	2007-2010	17,270	1,137	7	785	5	352	2
Breast	1994-1997	13,623	936	7	143	1	793	6
	1998-2001	15,145	1,001	7	172	1	829	5
	2002-2006	20,348	1,223	6	314	2	909	4
	2007-2010	19,893	629	3	236	1	393	2
Prostate	1994-1997	6,041	1,034	17	308	5	726	12
	1998-2001	7,774	1,602	21	352	5	1,250	16
	2002-2006	13,588	2,181	16	652	5	1,529	11
	2007-2010	15,454	1,124	7	325	2	799	5

Table 2. One-, three-, and five-year survival estimates with 95% confidence interval (CI) after bone metastasis diagnosis (all) by primary cancer type

	1-Year survival % (95% CI)	3-Year survival % (95% CI)	5-Year survival % (95% CI)
Digestive organs			
Colon*	21 (18 - 25)	7 (5- 10)	3 (2 - 5)
Rectum	22 (18 - 26)	3 (2- 5)	2 (1 - 3)
Respiratory organs			
Lung	10 (9- 11)	2 (1- 2)	1 (0.5 - 1)
Malignant Melanoma	17 (12 - 22)	6 (4-10)	5 (3 - 8)
Breast	51 (50 - 53)	25 (23- 26)	13 (11 - 14)
Female genital organs			
Cervix	18 (11-28)	6 (2-14)	2 (0-7)
Ovary	33 (21-44)	15 (7-25)	8 (3-18)
Male genital organs			
Prostate	35 (34 - 37)	12 (11 - 13)	6 (5- 7)
Urinary organs			

Kidney	29	10	5
	(26- 33)	(8 - 12)	(4 - 7)
Bladder	13	5	3
	(11 - 17)	(3 - 7)	(1 - 5)

* including colonrectosigmoid

Table 3. Median age (years) at bone metastasis diagnosis, and median time (days) since primary cancer to bone metastasis by primary cancer type stratified on bone metastasis only or bone metastasis plus other synchronous metastasis. Patients with bone metastasis at or within 3 months of primary cancer diagnosis were excluded.

	N	Median age, years, at diagnosis, (IQR)	Median time, days, from primary cancer diagnosis to bone met only (IQR)	Median time, days, from primary cancer to Bone metastasis + other synchronous metastases (IQR)
Digestive organs				
Colon (incl rectosig.)	355	68 (60-76)	748 (341-1429)	778 (495-1216)
Rectum	349	68 (60-76)	870 (414-1426)	1193 (500-1806)
Respiratory organs				
Lung	1239	66 (59-73)	295 (175-564)	279 (167-541)
Malignant Melanoma	225	64 (61-73)	784 (437-1703)	961 (454-1872)
Breast	2924	63 (54-72)	1246 (336-2151)	1432 (451-2309)
Female genital organs				
Cervix	64	52 (45-65)	723 (473-1520)	574 (491-1229)
Ovary	54	62 (51-68)	784 (444-1405)	987 (463-2572)
Male genital organs				
Prostate	4304	74 (68-80)	767 (411-1422)	748 (403-1352)
Urinary organs				
Kidney	346	66 (58-73)	545 (243-1306)	668 (60-1599)
Bladder	438	71 (64-77)	463 (260-1027)	610 (336-999)

Table 4. Hazard ratios (HR), and corresponding 95% confidence intervals for mortality after bone metastasis, comparing patients with bone metastasis only and patients with additional synchronous metastases.

Primary cancer		N (%)	Median survival time (days)	HR (95% CI)	Adjusted* HR (95%CI)
Colon cancer	Bone metastasis only	452 (91)	105	1.0	1.0
	Bone + other synchronous metastases	47 (9)	95	1.38 (1.02 - 1.87)	1.48 (1.09 - 2.03)
Rectum cancer	Bone metastasis only	361 (90)	114	1.0	1.0
	Bone + other synchronous metastases	39 (10)	79	1.47 (1.06 - 2.05)	1.44 (1.03 - 2.03)
Lung cancer	Bone metastasis only	2,871 (84)	74	1.0	1.0
	Bone + other synchronous metastases	532 (16)	61	1.20 (1.10 - 1.32)	1.27 (1.16 - 1.40)
Malignant melanoma	Bone metastasis only	172 (64)	95	1.0	1.0
	Bone + other synchronous metastases	97 (36)	75	1.26 (0.97 - 1.63)	1.29 (0.99 - 1.69)
Breast cancer	Bone metastasis only	3,268 (86)	377	1.0	1.0
	Bone + other synchronous metastases	521 (14)	170	1.42 (1.28 - 1.57)	1.47 (1.33 - 1.63)
Cervix cancer	Bone metastasis only	67 (91)	98	1.0	1.0

Primary cancer		N (%)	Median survival time (days)	HR (95% CI)	Adjusted* HR (95%CI)
	Bone + other synchronous metastases	7 (9)	46	1.06 (0.48 - 2.33)	1.00 (0.42 - 2.38)
Ovarian cancer	Bone metastasis only	54 (83)	170	1.0	1.0
	Bone + other synchronous metastases	11 (17)	129	1.12 (0.56 - 2.23)	1.08 (0.51 - 2.29)
Prostate cancer	Bone metastasis only	5,726 (96)	210	1.0	1.0
	Bone + other synchronous metastases	215 (4)	109	1.55 (1.35 - 1.78)	1.57 (1.36 - 1.80)
Kidney cancer	Bone metastasis only	609 (77)	182	1.0	1.0
	Bone + other synchronous metastases	186 (23)	105	1.33 (1.12 - 1.58)	1.41 (1.18 - 1.69)
Urinary bladder cancer	Bone metastasis only	513 (94)	68	1.0	1.0
	Bone + other synchronous metastases	33 (6)	56	1.14 (0.79 - 1.65)	1.22 (0.84 - 1.77)

* Adjusted by gender, age, Charlson Comorbidity Index Score, and period of diagnosis

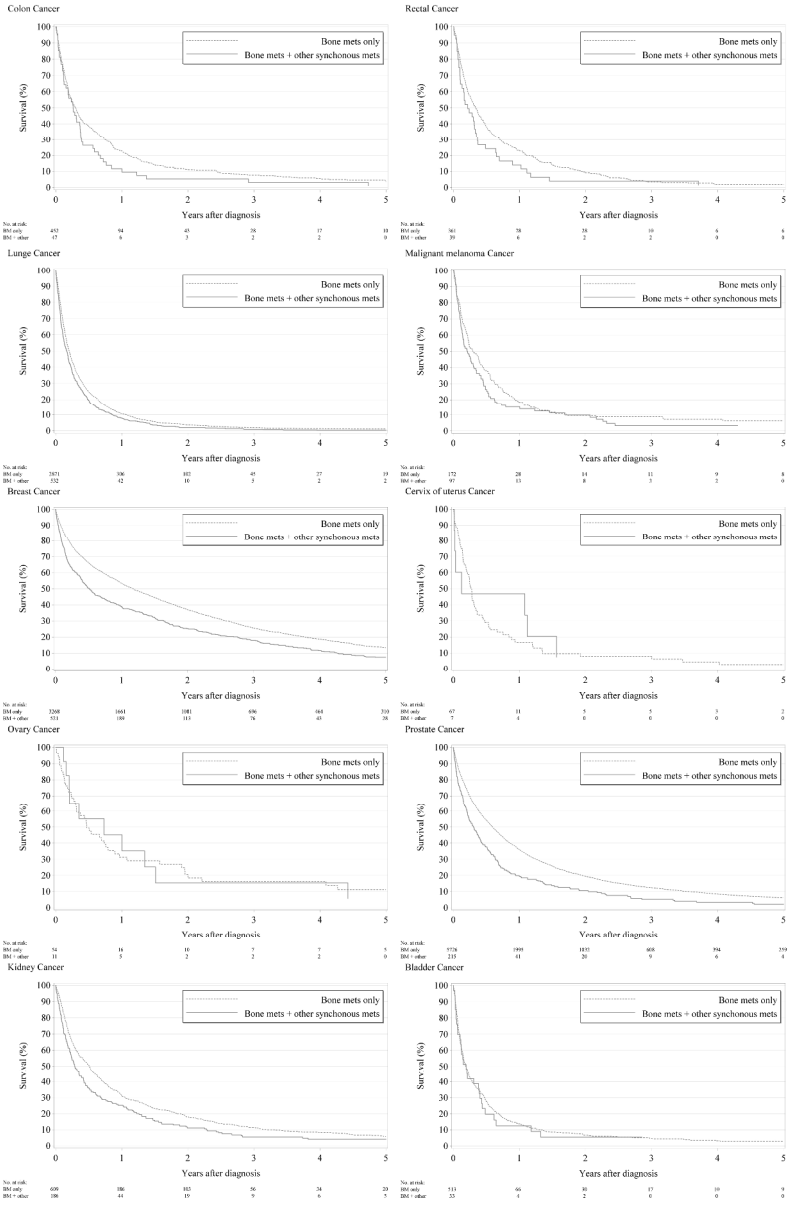

Figure 1

344x522mm (300 x 300 DPI)

Appendix : International classification of diseases (ICD-10) codes used in the current study

	ICD-10
Bone metastasis	C79.5
Any tumour	C00-C79
Other metastases present	C79.0-C79.9
Charlson Comorbidity Index conditions:	
Myocardial infarction	I21;I22;I23
Congestive heart failure	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45; G46
Dementia	F00-F03; F05.1; G30
Chronic pulmonary disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	K22.1; K25-K28
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0

Diabetes, Type 1	E10.0, E10.1; E10.9
Diabetes, Type 2	E11.0; E11.1; E11.9
Hemiplegia	G81; G82
Moderate to severe renal disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end-organ damage,	
Type 1	
Type 2	E10.2-E10.8
	E11.2-E11.8
Any tumor	C00-C75
Leukemia	C91-C95
Lymphoma	C81-C85; C88; C90; C96
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	C76-C80
AIDS	B21-B24

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation		Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3		
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4		We hypothesize that survival for other cancers will follow the above mentioned pattern, being better when no synchronous metastases are observed.
Methods					
Study design	4	Present key elements of study design early in the paper	5		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6		
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6		
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment	*6*		

measurement		(measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	5-6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a.
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Referred to
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 + tables
		(*b*) Report category boundaries when continuous variables were categorized	8 + tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.