Title: Identifying skeletal-related events for prostate cancer patients in routinely collected hospital data.

Short Title: Skeletal-related events in prostate cancer.

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ABSTRACT:

Background:

Non-osteoporotic skeletal-related events (SREs) are clinically important markers of disease progression in prostate cancer. We developed and validated an approach to identify SREs in men with prostate cancer using routinely-collected data.

Methods:

Patients diagnosed with prostate cancer between January 2010 and December 2013 were identified in the National Prostate Cancer Audit, based on English cancer registry data. A coding framework was developed based on diagnostic and procedure codes in linked national administrative hospital and routinely-collected radiotherapy data to identify SREs occurring before December 2015. Two coding definitions of SREs were assessed based on whether the SRE codes were paired with a bone metastasis code (*'specific definition'*) or used in isolation (*'sensitive definition'*). We explored the validity of both definitions by comparing the cumulative incidence of SREs from time of diagnosis according to prostate cancer stage at diagnosis with death as a competing risk.

Results:

We identified 40,063, 25,234 and 13,968 patients diagnosed with localised, locally advanced and metastatic disease, respectively. Using the specific definition, we found that the 5-year cumulative incidence of SREs was 0.8% in patients with localised disease, 6.0% in patients with locally advanced disease, and 42.2% in patients with metastatic disease. Using the sensitive definition, the corresponding cumulative incidence figures were 9.0%, 14.9%, and 44.3%, respectively.

Conclusion:

The comparison of the cumulative incidence of SREs identified in routinely collected hospital data, based on a specific coding definition in patients diagnosed with different prostate cancer stage, supports their validity as a clinically important marker of cancer progression.

KEYWORDS:

Metastatic prostate cancer; skeletal-related events; palliative radiotherapy; spinal cord compression; pathological fracture; surgery for bone metastases

1. INTRODUCTION:

Prognostic or therapeutic determinants of the outcomes of prostate cancer patients often need a long follow-up period due to the natural history of this disease, which may be protracted. In order to report on patient survival a long follow-up is required. Markers of disease progression – or disease recurrence after initial successful treatment – could therefore be attractive alternative outcomes because they occur earlier in the course of the disease (1).

National or regional cancer registries are highly effective at identifying patients who have been diagnosed with cancer but they often fail to recognise patients whose cancer has progressed or recurred. This is also true of many cancer trials, where long-term follow up is often restricted, resulting in a failure to detect events that occur late in the course of the disease. Administrative hospital data in the United States and Denmark have been used to identify one of the key progression markers in prostate cancer, non-osteoporotic skeletal-

related events (SREs) (2-7). These encompass pathological fractures, spinal cord compression, radiotherapy for bone metastases, or bone surgery. This highlights the possibility of using this measured event as a marker of disease progression or recurrence, allowing for an observation of the true natural history of prostate cancer, and as a clinically important event in its own right.

We developed a coding framework in data available in the National Prostate Cancer Audit to identify non-osteoporotic SREs in routinely collected hospital data, consisting of three national datasets linked at patient level. We validated this framework firstly by assessing how often identified SREs were 'paired' with a diagnosis code for bone metastasis, secondly by estimating the 5-year cumulative incidence of SREs according to prostate cancer stage at the time of diagnosis, and thirdly by comparing the incidence of SREs observed with our coding framework against results of other studies.

2. MATERIAL AND METHODS:

2.1 Patient population

We identified 152,851 men diagnosed with prostate cancer between January 1, 2010 and December 31, 2013 in the National Prostate Cancer Audit (8), according to the International Classification of Diseases, 10th Edition (ICD-10) code for prostate cancer (C61) (9) available in English cancer registry data. Men were categorised according to their cancer stage at the time of diagnosis (localised, locally advanced, or metastatic prostate cancer), according to a method developed by the National Prostate Cancer Audit (10). This categorisation is based on criteria recommended by the UK National Institute for Health and Care Excellence (11). It

uses Gleason score and TNM stage items that are available in the English cancer registry. Patients with M1 were categorised as having metastatic disease and in the remaining patients anyone with N1, T stage ≥3, Gleason score ≥8 or PSA >20 were categorised as having locally advanced disease. The cancer registry also provided the date of diagnosis.

The cancer registry dataset was linked to the Hospital Episode Statistics (HES) database (12), an administrative database of all hospital episodes in the English NHS (also including mortality data from the Office for National Statistics) and to the National Radiotherapy Dataset (RTDS) (13), a database of all radiotherapy treatment episodes in England. Follow-up was available up to December 31, 2015. Diagnosis codes in HES are based on ICD-10 codes and procedure codes according to the fourth revision of the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) (14). Men with missing data for cancer stage at the time of diagnosis (n = 63,586) were excluded (**Figure 1**).

2.2 Coding philosophy

Men who develop metastatic disease cannot reliably be identified as such in the English cancer registry or HES database because they are not always admitted to hospital and if admitted, the presence of metastatic disease is not always recorded. For that reason, we aimed to identify the first occurrence of a SRE, given that it is a serious complication of metastatic prostate cancer that typically results in a hospital-related treatment episode. The cumulative incidence of SREs underestimates the overall rate of disease progression, but it is likely to be a reliable and robust reflection of a clinically important, serious and costly complication of metastatic disease.

Our coding framework detects non-osteoporotic SREs in three ways. First, we identified diagnosis codes in HES for 'pathological fractures' or 'spinal cord compression'. Second, we identified procedure codes in HES for 'bone surgery'. Third, we identified codes in the linked RTDS to identify palliative radiotherapy.

2.3 Diagnosis codes

Based on earlier studies, a comprehensive a priori list of diagnosis codes related to SREs was generated. This list was informed by previous publications (15) and expert input from the co-authors who had a range of clinical backgrounds (MGP, AS, PC, HP, NC, AA). This step is termed *'forward coding'*. Codes for osteoporosis with pathological fractures (M800-9) were not included within this forward coding step in order to include only pathological fractures caused by bone metastases and not those solely caused by osteoporosis (given that men with prostate cancer are at risk of both). This is particularly relevant in light of the recent findings of the ERA-223 trial which set out to investigate the combination effect of adding radium-223 to abiraterone acetate and prednisolone/prednisolone in patients with castration-resistant metastatic prostate cancer. Radium-223 was shown to be contributing to an increased risk of osteoporotic fractures and led to the exclusion of osteoporotic events in this study (16).

The records of the hospital episodes in the HES database, identified through forward coding, were explored for additional common diagnosis codes that are likely to be related to a SRE. Diagnosis codes found through this step of *'backward coding'* were added to the code list. Backward coding was used because it is likely to add codes that are able to capture the idiosyncrasies of real-world coding practice that are difficult to identify otherwise. Expert

input from the co-authors was again used to ensure that inclusion of these additional codes was appropriate.

2.4 Procedure codes

In an earlier study (14) forward coding, was used to identify procedure codes related to surgery for bone metastases in the HES data set. Backward coding was also used to search for additional procedure codes.

2.5 Radiotherapy codes

Linkage to the RTDS was used to identify patients who had undergone radiotherapy for prostate cancer. Men were considered to have undergone radiotherapy to metastatic sites if in linked RTDS records the treatment region was coded as 'metastasis', if the treatment intent was coded as 'non-curative' and treatment region was missing, or if a radiotherapy episode occurred after a hospital episode in the HES database that included a diagnosis code for bone metastasis ('secondary malignant neoplasm of bone and marrow' [C795]). We only used a single code for bone metastasis (C795) for this purpose because other possible diagnosis codes for bone metastases ('malignant neoplasm of vertebral column' (C412) or 'malignant neoplasm of pelvic bones, sacrum and coccyx' (C414)) were never observed.

2.6 Validation

We validated the coding framework in three steps. First, we looked at how often diagnosis and procedure codes related to a SRE were 'paired' with the diagnosis code for bone metastasis (C795) in the same hospital episode in the HES database. In the cases where the SRE was identified in the RTDS, pairing was defined as the occurrence of a diagnosis code for

bone metastasis in a hospital episode which was within 6 months of the palliative radiotherapy start date as recorded in the RTDS. This step reflects that we can distinguish two coding definitions: a 'specific definition' in which the SRE codes are paired with a code for bone metastasis, and a 'sensitive definition' in which SRE codes are used in isolation.

Second, we investigated the association of the cumulative incidence of SREs after prostate cancer diagnosis with cancer stage at the time of diagnosis. Third, we compared the incidence of SREs, observed with our coding framework, with the results of other studies.

2.7 Statistical analysis

The 5-year cumulative incidence of SREs was estimated, with death being treated as a competing event (17). Men were followed up from the date of their prostate cancer diagnosis until their first SRE or until December 31, 2015, whichever came first. The data analysis was undertaken using Stata version 15 (StataCorp LLC, College Station, TX, USA).

3. RESULTS:

3.1 Coding framework to identify SREs in administrative hospital data and routinely-collected radiotherapy data

We included 79,265 men of whom 40,063 had localised disease, 25,234 had locally advanced disease, and 13,968 had metastatic disease at the time of diagnosis. The cohort was followed up and SREs were identified based on the coding framework generated through forward coding. Using the records of patients identified as having a SRE in this way, we identified two further diagnosis codes through backward coding: 'fracture of bone in

neoplastic disease' (M907) and 'myelopathy in disease classified elsewhere' (G992). The final list for SRE codes included in the coding framework is summarised in **Table 1**.

3.2 Validation

Table 2 shows how frequently the SRE-related diagnosis codes were paired with a bone metastasis code (C795), according to prostate cancer stage at diagnosis. These frequencies were high for patients with metastatic disease (all above 80%). They were lower for patients with localised or locally advanced disease, especially for the diagnosis codes with less specific definitions, including 'collapsed vertebra, not elsewhere classified' (M485), 'unspecified disease of spinal cord' (C958), 'other specified disease of spinal cord' (C959), and 'myelopathy in diseases classified elsewhere' (C992).

The surgical procedure codes were also frequently paired with a code for bone metastasis in men with metastatic disease at diagnosis (on average 75.4%). This frequency was again considerably lower in men with localised or locally advanced disease, which can be explained by the broad definitions of the included procedure codes for bone surgery.

The linked RTDS records indicating radiotherapy for metastasis were paired with a bone metastasis code in 78.4% of men with metastatic disease at diagnosis. Lower frequencies were again observed in men with localised or locally advanced disease.

These results demonstrate that a sensitive coding definition of SREs (SRE codes used without the requirement for pairing with a bone metastasis code) can lead to a substantial overestimation of the occurrence of skeletal events, especially in men diagnosed with

localised or locally advanced disease. For example, we found that the 5-year cumulative incidence of SREs for men diagnosed with metastatic disease was very similar, irrespective of whether the sensitive definition (44.3%) or the specific definition (42.2%) was used (**Table 3** and **Figure 2**). However, the difference in the cumulative incidence of SREs according to whether a sensitive or specific definition was used was much larger for men with localised disease (0.9% and 0.8%, respectively) and locally advanced disease (14.9% and 6.0%, respectively).

3.3 Further exploration of the diagnosis and procedure codes related to SRE

According to the specific coding definition of SREs, where SRE codes required pairing with a bone metastasis code, the majority of men who experienced a pathological fracture, spinal cord compression or both had some form of surgical and/or radiation-based intervention (77.1%, 86.0% and 93.7%, respectively; **Table 4**). In men diagnosed with metastatic prostate cancer, the most common SRE was radiotherapy for bone metastases with a 5-year cumulative incidence of 38.4%. The corresponding figures for pathological fractures, spinal cord compression and bone surgery were 6.6%, 10.3% and 6.4%, respectively.

4. DISCUSSION:

4.1 Overview

A coding framework was developed to identify non-osteoporotic SREs in men diagnosed with prostate cancer based on diagnosis codes (for pathological fractures and spinal cord compression) and procedure codes (for bone surgery) in administrative hospital data, and palliative radiotherapy codes in a routinely collected radiotherapy dataset.

We demonstrated that a specific coding definition for a SRE (requiring a paired diagnosis code for bone metastasis) produced a very similar 5-year cumulative SRE incidence in men with metastatic disease, at the time of their prostate cancer diagnosis, as a sensitive coding definition (not requiring a paired diagnosis code for bone metastasis). However, the 5-year cumulative incidences were much lower for patients with localised or locally advanced disease at diagnosis when the specific coding definition was used as opposed to the sensitive coding definition. These results suggest that the true-positive detection rates of SREs with specific and sensitive coding definitions are almost the same but that the false-positive detection rate with the specific coding definition is much lower than that of the sensitive coding definition.

4.2 Comparison with other studies

Comparing the incidence of SREs observed with our coding framework against results of other studies is the third step of the validation process. Our study is the largest study to report on the incidence of SREs in prostate cancer and is the first to do so in the UK using national population-based data for almost 80,000 patients with prostate cancer. We found that 39% of men with metastatic prostate cancer at the time of diagnosis experienced at least one SRE within 5 years. Six observational studies have used large administrative datasets to report on SREs in metastatic prostate cancer (2-7). Five of these studies have been conducted in the US (2-4, 6, 7) and four of these five used linked SEER-Medicare data (2-4, 6). The most recent of these studies was published in 2016 and used ICD-9 diagnosis codes and Healthcare Common Procedure Coding System (HCPCS) procedure codes to identify SREs in 3297 men diagnosed with metastatic disease between 2004 and 2009 (2). The coding framework used in this study compared well to the one used in ours but the

authors could not specify the target of radiotherapy. 40% of the men in this study experienced at least one SRE during a median follow-up of 19 months.

Similar results, also based on linked SEER-Medicare data, were shown for a cohort of 4404 men diagnosed with metastatic prostate cancer between 2005 and 2009 (44% experienced SREs after a median follow-up of 16.6 months) (3) and for a similar cohort of 9746 men diagnosed between 1999 and 2005, 44% experienced SREs after a median follow-up of 26 months) (4).

The fourth study that used SEER-Medicare data explored the impact of varying definitions of SREs in 8997 patients diagnosed between 2000 and 2009 (6). This study demonstrated that the observed SRE incidence depended on the codes included in the coding framework (specific versus sensitive codes), with codes used to identify pathological fractures being the most affected by differing definitions of a SRE. SRE incidence ranged from 46% ('base case' SRE definition) to 43% ('alternative' SRE definition) after a median follow-up of 18 months. The base case and alternative definitions differed with respect to the use of combinations of more sensitive and more specific definitions for the various SRE-related diagnoses and procedures.

The fifth US study included 3919 men diagnosed with bone metastases between 2002 and 2011 and recorded in the Thomson MedStat MarketScan Commercial Claims and Encounters database. A higher SRE rate was reported at 53% after a median follow-up of 16.1 months (7).

Finally, a Danish study analysed 3261 men diagnosed with bone metastases between 1999 and 2007 and reported similarly high SRE rates (cumulative incidence of 46.1% at 1 year and 53.8% at 5 years) (5).

We found a lower incidence of SREs than the six studies described above. An important explanation for this difference is that significant transitions have been made in the management of metastatic disease and that all patients included in our study were diagnosed in 2010 or later. New chemotherapeutic options have been shown to reduce the incidence of SREs and were not being used at the time of these older studies (18-22).

4.3 Methodological considerations

A major limitation of our work – and of all other studies in this area – is that we were reliant on the accuracy of the clinical coding in the routinely collected hospital data. However, the accuracy of these data has been shown to be high when compared to clinical notes and is sufficiently robust to support its use in research (23).

Incomplete information on cancer stage at the time of diagnosis is a further limitation because men with missing stage were excluded. We have previously shown that stage data is more often missing in prostate cancer patients older than 80 years and in those from a more socioeconomically deprived background (24). However, it is unlikely that this selective inclusion will have had a major impact on our results (comparing SRE incidence according to cancer stage at diagnosis), because there is no obvious plausible mechanism that would explain why cancer stage at diagnosis would have a different impact on the occurrence of SREs according to whether or not this information had been recorded.

Lastly, the use of administrative hospital data ensures that only severe events that require hospital events are captured. In this way, asymptomatic vertebral fractures are not identified with our coding framework which limits any potential over-estimation of the SRE incidence.

A key strength of our study is that the administrative hospital data and the routinely collected radiotherapy data are likely to have identified the majority of the relevant hospital and radiotherapy episodes. This is because more than 95% of patients diagnosed with prostate cancer in England are treated in the NHS, making it a nationally representative patient cohort. Furthermore, it is extremely rare that patients who have had their initial treatment in the English NHS will switch to a private healthcare provider later in their treatment pathway and this minimises underestimation of the SRE incidence due to loss to follow-up (28).

A unique feature of our study is that we compared the cumulative incidence of SREs according to prostate cancer stage at the time of diagnosis. This comparison allowed us to compare the performance of specific and sensitive coding definitions allowing for an assessment of coding consistency. The preference to use the specific coding definition of SREs, where SRE codes require pairing with a bone metastasis code, prevents substantial misclassification and overestimation of SREs and adds to the reliability of the coding framework.

Lastly, by using backward coding we created greater certainty that our coding framework also included diagnosis and procedure codes that are difficult to determine a priori. Two

frequently occurring diagnosis codes were added to our coding framework which will have further reduced the extent to which our approach underestimates the SRE incidence.

4.4 Implications

It is the first time that an administrative hospital database using ICD-10 diagnosis codes has been used to detect patients with a SRE. Given our explicit and transparent coding framework, our results are reproducible and applicable to other national administrative databases that use the same diagnosis codes and related procedure codes. Equally a similar coding framework could be applied to other cancer groups. Based on these results, we recommend that the specific coding definition for a SRE (requiring a paired diagnosis code for bone metastasis) is used in large-scale studies of routinely collected data to identify disease progression and compare treatment outcomes in prostate cancer.

In many countries, cancer registries are highly accurate and complete in identifying patients diagnosed with cancer, but their performance is considerably poorer in identifying disease progression. We have shown, along with studies from outside the UK, that administrative hospital data can be used to this end. The coding framework outlined in this paper can be used to detect SREs as a key outcome for comparisons of prostate cancer treatments. Capturing events other than death is important in order to measure highly relevant clinical outcomes which happen earlier so that a shorter follow-up is required for studies of therapeutic outcomes in prostate cancer patients.

The treatment options for metastatic prostate cancer are rapidly developing and now chemotherapy, in the neoadjuvant and castrate-resistant settings, is able to reduce the

incidence of SREs and prolong survival (30). The ability to identify the occurrence of SREs in a 'real-world' national population is paramount in order to describe disease trends and assess the impact of novel treatments and their value (31).

5. CONCLUSIONS:

Combinations of diagnosis and procedure codes in administrative hospital data linked to a national radiotherapy dataset can be used to identify non-osteoporotic SREs across cancer stages. Identifying SREs based on these codes provides an accurate measure of cancer progression which can be used for comparing treatment outcomes in routinely collected hospital data according to prognostic or therapeutic determinants.

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Figure 1.
Flow chart of men included in the study.

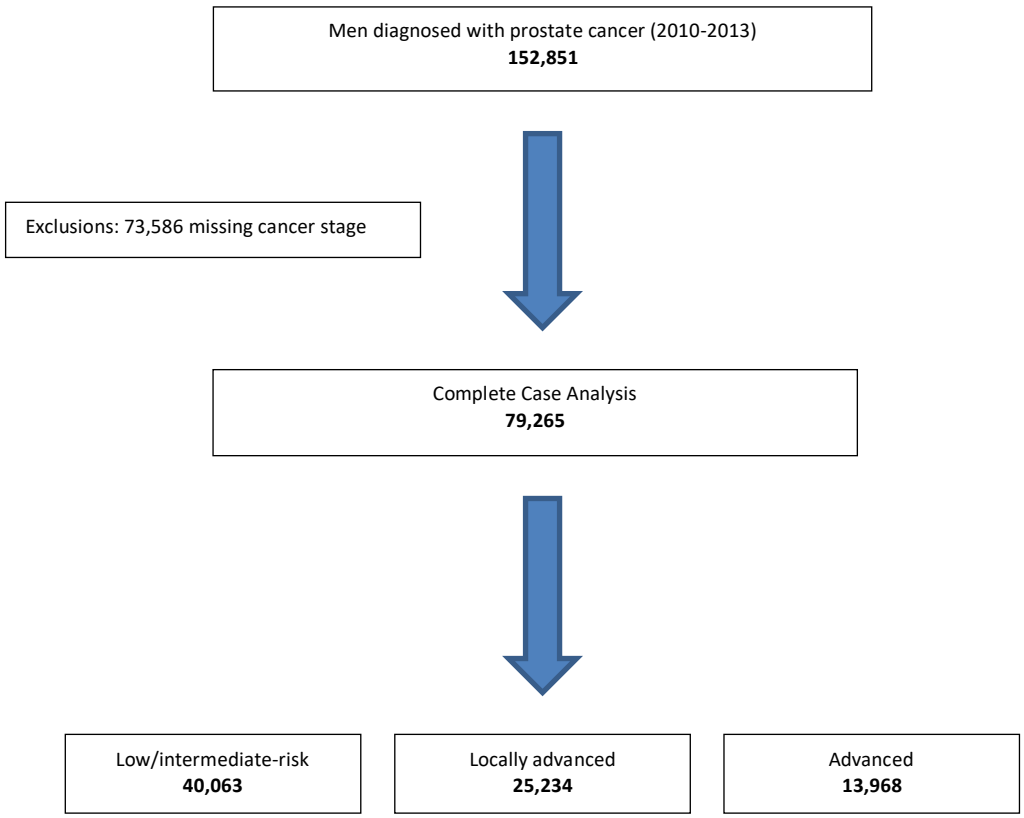

Figure 2.
Cumulative incidence of the first occurrence of a skeletal-related event in men with prostate cancer, according to the specific definition, stratified by cancer stage at diagnosis.

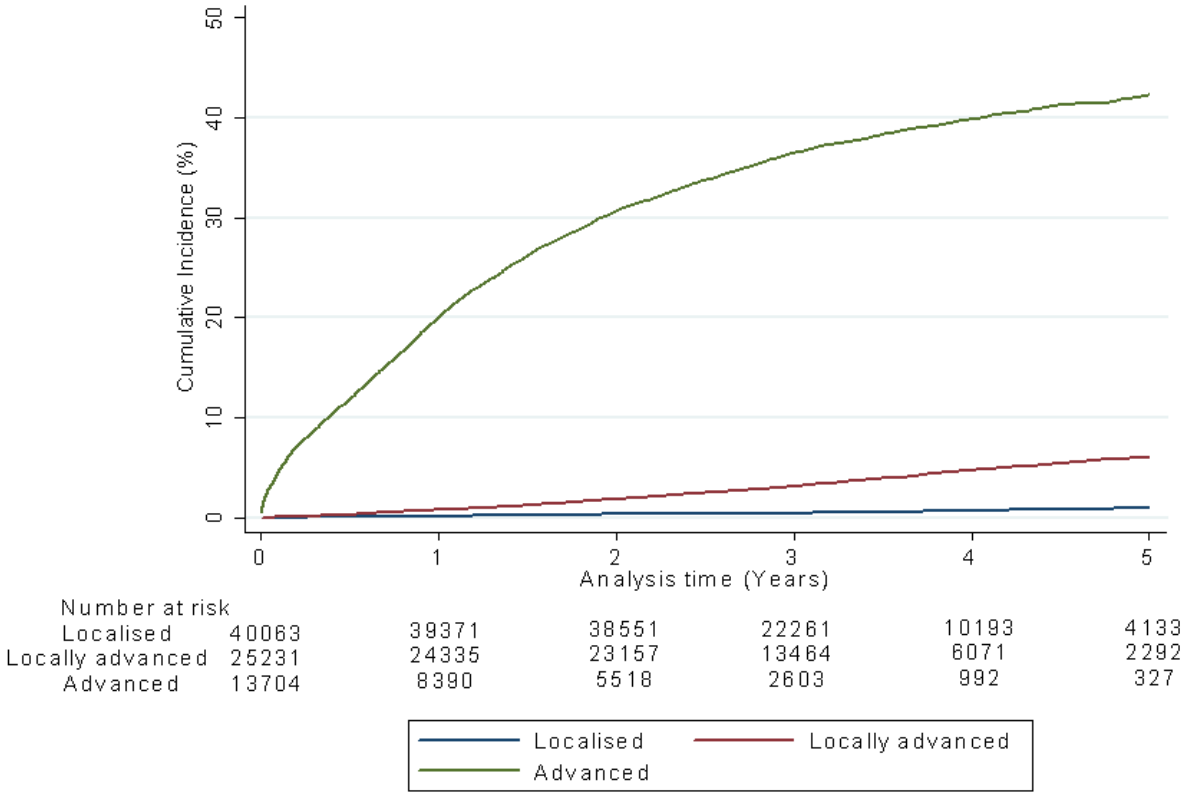

Table 1.
ICD-10 diagnosis code and OPCS-4 procedure code definitions for skeletal-related events.

	Code Definition
ICD-10 diagnosis codes	
Pathological fracture	
M485	Collapsed vertebra, not elsewhere classified
M495	Collapsed vertebra in diseases classified elsewhere
M844	Pathological fracture, not elsewhere classified
M907*	Fracture of bone in neoplastic disease
Spinal cord compression	
G550	Nerve root and plexus compressions in neoplastic disease
G834	Cauda equine syndrome
G952	Other and unspecified spinal cord compression
G958	Unspecified disease of spinal cord
G959	Other specified disease of spinal cord
G992*	Myelopathy in diseases classified elsewhere
OPCS-4 procedure codes	
Spinal surgery	
V22-7, V67-8	Decompression operations on spine
V28	Insertion of lumbar interspinous process spacer
V38-4	Fusion of joint/stabilisation of spine
V41	Instrumental correction of deformity of spine
V43, V47	Extirpation of lesion/biopsy of spine
V44-6,	Decompression/reduction/fixation of fracture of spine
V55	Levels of spine
Bone surgery	
W05	Prosthetic replacement of bone
W08-9	Excision of bone/extirpation of lesion of bone
W16	Division of bone
W19-26	Reduction of fracture
W28, W30	Internal/external fixation of bone
W37-41, W93-5	Replacement of hip/knee joint
W46-8	Prosthetic replacement of head of femur
W65-7	Reduction of traumatic dislocation of joint

* Codes identified through 'backward coding'. See Material and Methods for further explanation.

Table 2.

Frequency of the first occurrence of codes for skeletal-related events with and without a diagnosis code for bone metastasis, stratified by prostate cancer stage at diagnosis.

First occurrence of a SRE* code per man	Prostate cancer stage at diagnosis					
	Metastatic		Locally advanced		Localised	
	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)	SRE paired with bone metastasis n (%)	SRE not paired with bone metastasis n (%)
DIAGNOSIS CODES						
Pathological fracture codes						
Any code (n=1313)	918 (95.8)	40 (4.2)	146 (62.4)	88 (37.6)	51 (42.2)	70 (57.9)
M485 (n=206)	62 (80.5)	15 (19.5)	13 (17.8)	60 (82.2)	7 (12.5)	49 (87.5)
M495 (n=294)	233 (99.6)	1 (0.4)	32 (88.9)	4 (11.1)	21 (87.5)	3 (12.5)
M844 (n=127)	57 (82.6)	12 (17.4)	9 (29.0)	22 (71.0)	7 (25.9)	20 (74.1)
M907 (n=794)	635 (97.2)	18 (2.8)	101 (91.8)	9 (8.2)	26 (83.9)	5 (16.1)
Spinal cord compression codes						
Any code (n=1848)	1409 (97.4)	37 (2.6)	181 (69.6)	79 (30.4)	55 (38.7)	87 (61.3)
G550 (n=441)	378 (99.0)	4 (1.1)	45 (97.7)	2 (4.3)	12 (100)	0 (0)
G834 (n=207)	161 (98.2)	3 (1.8)	26 (84.9)	5 (16.1)	5 (41.7)	7 (58.3)
G952 (n=661)	505 (93.5)	35 (6.5)	62 (74.8)	22 (26.2)	20 (54.1)	17 (46.0)
G958 (n=32)	11 (84.6)	2 (15.4)	3 (16.7)	15 (83.3)	1 (9.1)	10 (90.9)
G959 (n=50)	21 (87.5)	3 (12.5)	3 (42.9)	42 (31.1)	0 (0)	8 (100)
G992 (n=983)	748 (97.7)	18 (2.4)	93 (68.9)	4 (4.1)	28 (34.2)	54 (65.9)
PROCEDURE CODES						
Surgery codes						
OPCS-4 V/W codes (n=5186)**	872 (75.4)	284 (24.6)	128 (7.4)	1603 (92.6)	43 (1.9)	2256 (98.1)
RTDS palliative radiotherapy codes*						
RT episodes with valid HES record**** (n=5115)	3795 (89.7)	438 (10.4)	585 (77.1)	174 (22.9)	89(72.4)	34 (27.6)

* Skeletal-related event; ** See Table 2; *** Radiotherapy Dataset; **** Only men with a HES record within 6 months of the start date of radiotherapy

Table 3.
Cumulative incidence of skeletal-related events according to prostate cancer stage at diagnosis for men with prostate cancer.

Cancer stage at diagnosis	5-year cumulative incidence (%)	95% CI	
Specific definition			
Localised	0.8	1.0	- 1.1
Locally advanced	6.0	5.5	- 6.4
Metastatic	42.2	41.2	- 43.3
Sensitive definition			
Localised	0.9	8.6	- 9.4
Locally advanced	14.9	14.3	- 15.6
Metastatic	44.3	43.3	- 45.4

Table 4.
Frequency that patients with pathological fractures and/or spinal cord compression, according to the specific definition, undergo bone surgery and/or palliative radiotherapy.

	Procedural skeletal-related event				
Diagnostic SRE skeletal event	Bone surgery n (%)	Radiotherapy n (%)	Both n (%)	Neither n (%)	Total n (%)
Pathological fracture	120 (15.9)	247 (32.8)	189 (25.1)	198 (26.3)	754 (100)
Spinal cord compression	37 (2.9)	924 (72.0)	131 (10.2)	192 (15.0)	1284 (100)
Both	26 (7.2)	195 (54.0)	119 (33.0)	21 (5.8)	361 (100)
Neither	225 (0.3)	3888 (5.1)	196 (0.3)	72,557 (94.4)	76,866 (100)
Total	408 (0.5)	5,254 (6.6)	635 (0.8)	72,968 (92.1)	79,265 (100)