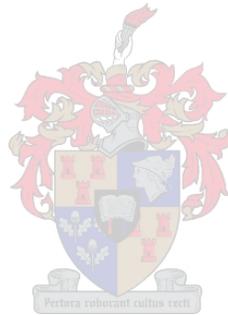


**Bone involvement**  
**in patients with cervical carcinoma –**  
**a single institution cohort study**

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**Thesis presented in partial fulfilment of the requirements for the degree of Master of Philosophy in  
Gynaecological Oncology**

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## **Declaration**

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## **Abstract**

### **Introduction**

Bony metastases in cervical carcinoma are rare, occurring on average in 4.6% of patients. Autopsy studies indicate that it is underdiagnosed. It is important to recognise bony infiltration as palliative radiotherapy can relieve pain and prevent pathological fractures. As survival after the diagnosis of bone involvement is short, an appropriate palliative care plan should be tailored according to the patients' limited prognosis.

### **Methods**

A retrospective cohort analysis of women with cervical cancer, diagnosed between January 2014 and December 2015, was undertaken. Demographic, treatment and follow up data were collected for all women with bone metastases confirmed by imaging. Descriptive statistics were generated.

### **Results**

The cohort study identified 642 patients with cervical carcinoma, of which 25 (3.89%) were diagnosed with bone involvement. Ten patients had bone involvement at diagnosis of cervical cancer and 15 had bone metastases at recurrence, occurring a median of 286 days after primary treatment.

Survival after the diagnosis of bone metastases was short, with 88% of patients dying within the first 6 months. Women with a low WHO performance status at diagnosis of bone metastases had a significantly shorter survival ( $p=0.024$ ). When a previously described prognostic score was applied, those with a high score had a significantly shorter survival (median 61 days) than those with a low score (median 158 days) ( $p=0.0065$ ).

### **Conclusions**

Although bone metastases are rare in women with cervical cancer, they are important to recognise as radiotherapy is a useful modality for palliating bone pain and reducing pathological fractures. Health care workers should be vigilant, especially during the first 2 years of follow up, to increased analgesic use and chronic pain as these may indicate bone involvement.

Use of a prognostic score is valuable in tailoring treatment and counselling patients and their families with regard to survival. Survival after the diagnosis of bone involvement is short and a patient's quality of life may be greatly improved by an appropriate radiotherapy and palliative care plan.

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## **Bone involvement in women with cervical cancer at Tygerberg Hospital**

### **Introduction**

Cervical cancer is the 2<sup>nd</sup> most common cancer in women after breast cancer in Sub Saharan Africa [1]. Many women in South Africa present with late stage disease, due to poor access to the cervical screening programme and lack of knowledge regarding the disease [2].

Metastases to bone or direct infiltration of cancer into bone, although rare, are important to recognize and diagnose as palliative radiotherapy treatment can then be timeously employed to relieve pain and improve quality of life. This information also assists in determining prognosis and life expectancy, and could be used to tailor appropriate treatment plans.

This descriptive study aims to describe the patient and tumour characteristics and treatment of cervical cancer patients with confirmed bone involvement at Tygerberg Hospital Gynaecologic Oncology Unit.

### **Prevalence**

In a review article, including 5 studies with a total 4422 cervical cancer patients, the prevalence of bone metastases ranged from 1.8% – 6.6 % with an average of 4.6% (205/4422) [3]. In a more recent study, Matsumiya et al. reported the prevalence of bone metastases in 5.8% (54/925) of women with cervical cancer treated between 1995 and 2014 at a cancer centre in Japan [4]. Two South African studies; the first of radiographic findings on 1347 women at cervical cancer diagnosis at Johannesburg General Hospital and the second, at Tygerberg Hospital, investigating the detection of bone metastases by bone scan at cervical cancer diagnosis in 540 patients; gave prevalences of bony involvement at diagnosis of 4.6% and 2.03% respectively [5,6]. A higher rate of bone involvement was reported at an autopsy study of bone metastasis in all gynaecological cancers [7]. Of the 112 cervical cancer patients who were autopsied, 20 (17.9%) were found to have bony involvement. Of these only 7 (6.3%) had pre-morbid radiographic evidence of bone metastasis, indicating that it is likely underdiagnosed.

## Diagnosis

Most patients with bone metastases are diagnosed at recurrence of disease, however a few women have bone involvement at cancer diagnosis [8]. Since cervical cancer is clinically staged, routine imaging, other than a chest x-ray and abdominal ultrasound, is seldom performed at diagnosis in a resource limited setting. Follow up of treated cervical cancer patients includes a consultation and thorough physical examination. Between 25-50% of recurrences are detected at routine follow up visits, the rest are at diagnosed in patients presenting with symptoms [9]. Physical examination has the highest detection rate for recurrence when compared to cytology and imaging modalities. There are insufficient data to support routine use of imaging to detect recurrence [10]. Further investigations at diagnosis and follow up are performed based on abnormalities found at examination or on symptoms reported by the patient.

## Symptoms

Pain is the most common presenting symptom of patients with bony involvement [4,8]. Neurological deficit, pathological fracture and fatigue can be present in isolation or in combination with pain [8]. More than 50% of patients have extra skeletal metastases at time of diagnosis of bone metastasis, most frequently in the lung [8,11]. The most common sites for bone involvement are the lumbar spine followed by the pelvis, thoracic spine and ribs. Bone metastases have also been reported in the upper and lower extremities although this is rare [12,13].

There are 4 proposed mechanisms of metastasis to the skeleton: 1. Pelvic or parametrial tumour growth directly into the pelvic bones; 2. Direct extension from other soft tissue metastasis, such as lung into ribs or brain metastasis into skull; 3. Dissemination to the spine by way of Batson's venous plexus; 4. Distant haematogenous metastasis to extremities [3].

As mentioned before, imaging is not performed routinely at each follow up visit, however if patients have constant pain that is not responsive to analgesia, bony metastasis should be considered.

## Imaging

Plain x-rays are used as a first line investigation for detecting bony involvement because they are inexpensive and accessible, however sensitivity and specificity are low. A second investigation is usually required to confirm metastases [14]. Bone scintigraphy is useful for detecting bone pathology, and has the added advantage of imaging the whole skeleton, however it is not very specific. A historic study at Tygerberg hospital using bone scintigraphy to detect bony involvement at diagnosis of cervical cancer had a false positive rate of 8% (43/540 scans) and a pick-up rate of 2.03%. Degenerative and arthritic changes, congenital bone lesions, trauma and previous fractures were the most common explanations for the false positive results [6]. Brodowitz et al. published a recent review on the current recommendations for monitoring bone health in the cancer patient [14]. Table 1 shows the advantages and disadvantages of the various imaging modalities .

A small study of 20 patients compared axial MRI to whole body bone scintigraphy for detection of bone metastases in patients with solid tumours. They concluded that MRI was more sensitive and specific than bone scintigraphy for metastases in the spine, as well as providing information on tumour infiltration into structures surrounding the vertebrae, which impacts on therapeutic decisions. As bone scintigraphy included the entire skeleton, it was useful in detecting metastases outside of the spine in the appendicular skeleton [15].

Whole body MRI and whole body (18F)-2-fluoro-2-deoxyd-glucose (FDG) PET/CT were compared for diagnostic accuracy in detecting bone metastases in 109 patients with either malignant melanoma or small cell lung carcinoma. Metastases were detected in 10% (11/109) of patients and there was no significant difference in the diagnostic ability of the two imaging modalities [16].

In a retrospective study more specific to the detection of bone metastases in cervical cancer, Liu et al. compared CT scan and MRI to FDG-PET/CT [17]. They included 233 imaging pairs to compare CT and PET and 245 imaging pairs to compare PET with MRI. They found that PET was more sensitive than CT, and more specific than MRI. The other advantage of PET/CT is that lymph node metastases are also detected. Using multivariate analysis of risk factors (including age; FIGO stage; histological type; tumour differentiation and extent of lymph node involvement) for haematogenous bone metastases at primary staging, lymph node extent was the only significant predictor of bone metastases [17].

**Table 1. Advantages and disadvantages of imaging modalities for the detection of bone metastases**

Imaging modality	Advantages	Disadvantages
Plain radiography	<ul style="list-style-type: none"> <li>• Widely available and inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• Widely available and inexpensive</li> </ul>
Radionuclide bone scintigraphy	<ul style="list-style-type: none"> <li>• Relatively inexpensive</li> <li>• Evaluates whole skeletal system</li> <li>• Provides information on osteoblastic activity and skeletal vascularity</li> <li>• More sensitive than plain radiography</li> </ul>	<ul style="list-style-type: none"> <li>• Low specificity for bone metastases</li> <li>• Cannot directly detect osteolytic metastases</li> </ul>
CT	<ul style="list-style-type: none"> <li>• Higher resolution than plain radiography and provides three-dimensional anatomical information</li> <li>• Modality of choice for evaluating cortical bone (e.g. the ribs)</li> <li>• Excellent soft tissue and contrast resolution; soft tissue extension of bone metastases is easily visualized</li> <li>• Useful to localize lesions for biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Low specificity for bone metastases</li> </ul>
MRI	<ul style="list-style-type: none"> <li>• Higher resolution than plain radiography and additional three-dimensional anatomical information</li> <li>• Highly sensitive (95%) for detection of bone metastases</li> <li>• Multi-planar images permit imaging of the entire spine in the sagittal plane</li> <li>• Excellent for demonstrating bone marrow infiltration</li> <li>• Preferred imaging method for spinal cord compression and subsequent planning of surgery or radiation therapy</li> <li>• Superior to C-choline PET/CT for detecting bone metastases</li> </ul>	<ul style="list-style-type: none"> <li>• Not suitable for evaluating cortical bone</li> <li>• Cost-effectiveness of newer MRI modalities (e.g. whole-body or axial MRI) unclear</li> </ul>
SPECT	<ul style="list-style-type: none"> <li>• Superior sensitivity and specificity to bone scintigraphy</li> <li>• Axial slices provide better localization of radionuclide uptake than bone scintigraphy</li> </ul>	<ul style="list-style-type: none"> <li>• Cannot generate absolute quantification values</li> <li>• Whole-body scanning not possible in a reasonable time frame</li> <li>• Less widely available and more costly than other imaging modalities</li> </ul>
<sup>18</sup> F-DG-PET	<ul style="list-style-type: none"> <li>• Superior sensitivity to bone scintigraphy</li> <li>• Allows visualization of functional aspects</li> </ul>	<ul style="list-style-type: none"> <li>• Role in routine practice unclear</li> <li>• Less widely available and more costly than other imaging modalities</li> </ul>
<sup>11</sup> C-choline PET/CT	<ul style="list-style-type: none"> <li>• Higher specificity than bone scintigraphy and MRI, with fewer indeterminate lesions</li> </ul>	<ul style="list-style-type: none"> <li>• May not provide greater sensitivity than bone scintigraphy</li> <li>• Cost-effectiveness unclear</li> <li>• Less widely available and more costly than other imaging modalities</li> </ul>

*Abbreviations:* C, carbon; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Taken from Brodowicz, T., et al., Early identification and intervention matters: A comprehensive review of current evidence and recommendations for the monitoring of bone health in patients with cancer.

In a recent retrospective study, patients were selected based on positive histology from bone biopsy specimens. A total of 409 biopsies and 748 images were used to calculate the diagnostic characteristics of each of the different imaging modalities. A summary of the findings is shown in Table 2. Once again PET/CT and MRI were the top performing modalities, with MRI being more accurate for spine metastases and PET/CT more accurate for non-spine lesions [18].

**Table 2. Diagnostic characteristics of the imaging modalities (reported with 95% confidence intervals).**

	X-ray ( <i>n</i> = 223)	CT ( <i>n</i> = 233)	MRI ( <i>n</i> = 209)	BS ( <i>n</i> = 35)	PET/CT ( <i>n</i> = 58)
Sensitivity	33.0(23.6–43.6)	75.6(67.8–82.6)	90.5 (83.7–95.2)	74.1 (53.7–88.8)	92.3 (79.1–98.3)
Specificity	96.1 (91.2–98.7)	89.2 (81.1–94.7)	81.1 (73.6–89.8)	62.5 (24.7–91.0)	63.2 (38.4–83.7)
Accuracy	69.5 (63.0–75.5)	81.1 (75.5–85.9)	87.1 (81.8–91.5)	71.4 (53.7–85.4)	82.7 (70.6–91.4)
PPV	86.1 (70.5–95.3)	91.4 (84.7–95.8)	86.8 (79.4–92.2)	87.0 (66.4–97.1)	83.7 (69.3–93.2)
NPV	66.3 (59.1–73.0)	70.9 (61.8–79.0)	87.5 (78.7–93.6)	41.7 (15.3–72.3)	80.0 (51.9–95.4)

Abbreviations: negative predictive value (NPV); positive predictive value (PPV).

Taken from: Lange, M.B., et al., Diagnostic accuracy of imaging methods for the diagnosis of skeletal malignancies: A retrospective analysis against a pathology-proven reference.

### Risk factors

The risk of developing distant metastases after chemoradiation for cervical cancer was investigated by Schmid et al. The most important factors were lymph node involvement and FIGO stage of disease. Eleven percent of patients staged Ib to IIIa with negative nodes developed distant metastases with a 91% 3 year distant metastases-free survival (DMFS), while 38% of patients stage IIIb to IVa or with positive nodes developed distant metastases with a 67% 3 year DMFS. They also showed that in the group with positive nodes, the lower the number of chemotherapy cycles given during radiation the higher the risk for developing distant metastases. The number of chemotherapy cycles had no impact on metastases in the low risk group [19].

Poorly differentiated tumours and histological types other than squamous carcinoma, such as small cell neuroendocrine, clear cell and adenoid cystic carcinoma, were found to have a greater tendency to spread to bone in a retrospective study [3]. Advanced FIGO stage and a greater extent of lymph node metastases have both been linked to bone metastases. In univariate analysis of 165 cervical cancer

patients, FIGO stage and extent of lymph node metastases were both associated with the development of bone metastases, however only extent of lymph node metastases was significant on multivariate analysis. Patients with lymphatic spread to pelvic, para-aortic or inguinal nodes, supraclavicular, and mediastinal lymph nodes had a 2%, 6%, 11%, and 55% incidence of haematogenous bone metastases. There were no patients with bone metastases and negative nodes [17].

Risk factors associated with the earlier development of bone metastases in patients with cervical cancer were investigated by Yoon et al. Over a 17 year period they treated 2013 patients with cervical cancer of whom 105 developed bone metastases (5.21%). After multivariate analysis the risk factors that remained significant for shorter time to the development of bone metastases were advanced (IIb – IVb) vs early FIGO stage (I and IIa); Adenocarcinoma (vs Squamous and Adenosquamous) and if patients developed multiple bone metastases (vs single metastases). There was no significant difference in survival after the diagnosis of bone metastases (average 10 months) with any of these risk factors. Those patients who received salvage radiotherapy to the bone metastases had a longer survival than those that only received chemotherapy (12 versus 7 months) [11].

## Timeline

The median time from diagnosis of cervical cancer to onset of bone metastases varies from 16 months (range 2-203 months) to 27 months (range 0-279 months), with a wide range [8,11]. In 75% of patients, bone metastases develop within 3 years after diagnosis of cervix cancer [3]. Yoon et al. showed a significantly shorter time to develop bone metastases with adenocarcinoma than squamous cell carcinoma (12 vs 29 months;  $p=0.0016$ ) and with late stage disease versus early stage disease (15 vs 22 months;  $p=0.02$ ). Median survival after the diagnosis of bone metastases is short, ranging from 3.5 months to 17 months [3,11]. In one study 81% of patients died within 1 year and 95% within 2 years after bone metastases were detected [3]. Matsumiya et al. investigated factors which influence survival after the detection of bone metastases from cervical cancer. After multivariate analysis, 5 factors proved to be significant: Synchronous extraskkeletal metastasis; WHO performance status of 3 to 4; onset time at initial presentation (at diagnosis or recurrence); multiple bone metastases and a bone metastasis-free interval of less than 12 months. They used these 5 factors to develop a prognostic scoring system, where 1 point was allocated for each significant factor. The 26 week survival in patients with a score of 2 was 61.4% and

was only 12.5% for those with a score  $\geq 4$ . The median survival for those patients with a score of  $\geq 4$  was 13 weeks [4]. This information is very helpful in planning treatment, especially when it comes to spinal surgery for bone metastasis, where a 3-6 month life expectancy is a prerequisite.

## Treatment

Radiotherapy has been shown to be an effective palliative treatment for bone pain due to metastatic cancer [20]. There are many different radiotherapy regimes including single dose and multiple fraction protocols, with marked variation in the fractionation prescribed according to geographical location and practice setting (university/academic vs private) [21]. A Cochrane review investigated the efficacy of single fraction radiotherapy in comparison to multiple fraction radiotherapy for relieving bone pain from metastatic cancer. Eleven trials with 3435 patients were included in the systematic review. Complete pain relief was reported in one third of patients with partial pain relief in 60% of patients. There was no difference in efficacy in relieving bone pain between single fraction and multiple fraction regimes. There was also no difference between the risk of spinal cord compression with single or multiple fraction radiotherapy. Retreatment was higher in the single fraction group, although this was confounded by the fact that radiotherapists are less likely to retreat after giving multiple fractions. The risk of developing a pathological fracture was also slightly higher in the group that received single fraction radiotherapy (3% vs 1.7%) [22]. An update on this systematic review, including 25 trials, confirmed the results of the Cochrane review and suggested that single fraction radiotherapy should be implemented as standard of care for palliation of uncomplicated bone metastasis [23]. Taking into account the burden of a multiple fraction regime on the radiotherapy centre, the time and cost to the patient of attending for numerous treatments and the reduced life expectancy of these patients, it seems appropriate that a single fraction should be the standard protocol. Eight Gray as a single fraction is considered to be the most cost effective and convenient treatment with the least acute toxicity [24].

Recently a European panel issued a consensus guideline that advocates the use of bisphosphonates in early breast cancer, not only for bone health due to the use of tamoxifen, aromatase inhibitors and castration, but also for delaying onset of bone metastases [25]. In patients that already have skeletal metastases, bisphosphonates, such as Zoledronic acid, and target therapies, such as denosumab, are approved in Europe and United States for reducing skeletal related events (SRE's), including spinal cord compression, pathological fractures and vertebral collapse [26]. Studies on Zoledronic acid have shown

that it delays the time to SRE and reduces pain from bone metastases [27]. Most studies on bisphosphonates have been carried out in patients with breast, prostate and lung cancer where bone metastases are a common event, occurring in 65 – 75% of patients with breast or prostate cancer. Although bone involvement is rare in cervical cancer, bisphosphonates may play a role in reducing SRE's, palliating pain and improving quality of life.

Life expectancy after the development of bone metastases from cervical cancer is short, with 95% of patients dying within 2 years. It is important to identify risk factors that may reduce life expectancy, so that the treatment offered is of an appropriately short duration and offers maximal palliation. This study aims to study patients with bone metastases from cervical cancer at Tygerberg Hospital in order to identify common risk factors and tailor a more suitable follow up schedule for those who are at high risk.

## **Aims and Objectives**

- To estimate the prevalence of bone metastases occurring in patients with cervical cancer at Tygerberg Hospital.
- To describe the patient and cervical tumour characteristics in women with bone metastases.
- To identify common risk factors in patients with bone metastases in order to tailor their follow up schedule.
- To educate doctors treating patients with cervical cancer to be aware of the symptoms of bone metastases and of the value of palliative radiotherapy for pain relief by publication of a manuscript.

## **Methods**

This study is a cohort analysis of folders of patients with confirmed cervical cancer who attended the Tygerberg Gynaecology Oncology Unit for their initial visit between January 2014 and December 2015. Patients were identified from the gynaecological-oncology records, which were assessed for imaging studies which confirmed bone metastases. Their general folders, gynaecological-oncology and radiation oncology folders were accessed for further information and follow up data.

Patients were initially clinically staged together with basic imaging including chest x-ray, abdominal ultrasound and a cystoscopy to rule out bladder metastases. A CT scan was used for planning radiotherapy fields. The standard protocol of 45-50 Gray to the pelvis with concomitant weekly Cisplatin followed by 25 Gray given as brachytherapy to the cervix was offered to patients who were treated with curative intent. This protocol was modified for patients not tolerating treatment and for those treated with palliative intent. From 2015 onwards many patients with FIGO stage IIIb cervical cancer had PET/CT for radiotherapy planning.

Follow up consisted of a clinical examination and specific investigations based on the patients symptoms every 3 months for the first 2 years, 6 monthly for the next 3 years and then yearly. Data was censored on 15 January 2018.

Descriptive statistics, means, medians and ranges were reported. Means were compared using the T-test with significance set at 0.05. Kaplan Meier estimates were used for survival analysis and survival curves were compared using the Rank-log method. Statistics were analysed using Social Science Statistics

(<http://www.socscistatistics.com>), and the Real Statistics Resource Pack software, Release 5.4 ([www.real-statistics.com](http://www.real-statistics.com)) in Microsoft Excel 2010 was used to generate the Kaplan Meier estimates.

The study was approved by the University of Stellenbosch Health Research Ethics Committee (Reference number S17/10/258). The patients' names and any identifying characteristics remained confidential throughout the study, with only the principal investigator having access to the data list.

## Results

### Prevalence

642 newly diagnosed cervical cancer patients attended the Gynaecological Oncology Unit between 1 January 2014 and 31 December 2015. 25 patients (3.89%) were found to have radiological evidence of bone involvement. The mean age of women with bone metastases was 46 years (SD 11.28) with a range from 25 to 63 years. Six women were found to have bone involvement at initial staging and 4 women at imaging during radiotherapy treatment planning. The remaining 15 patients had bone metastases at recurrence. Their clinical details are found in table 3 and 4.

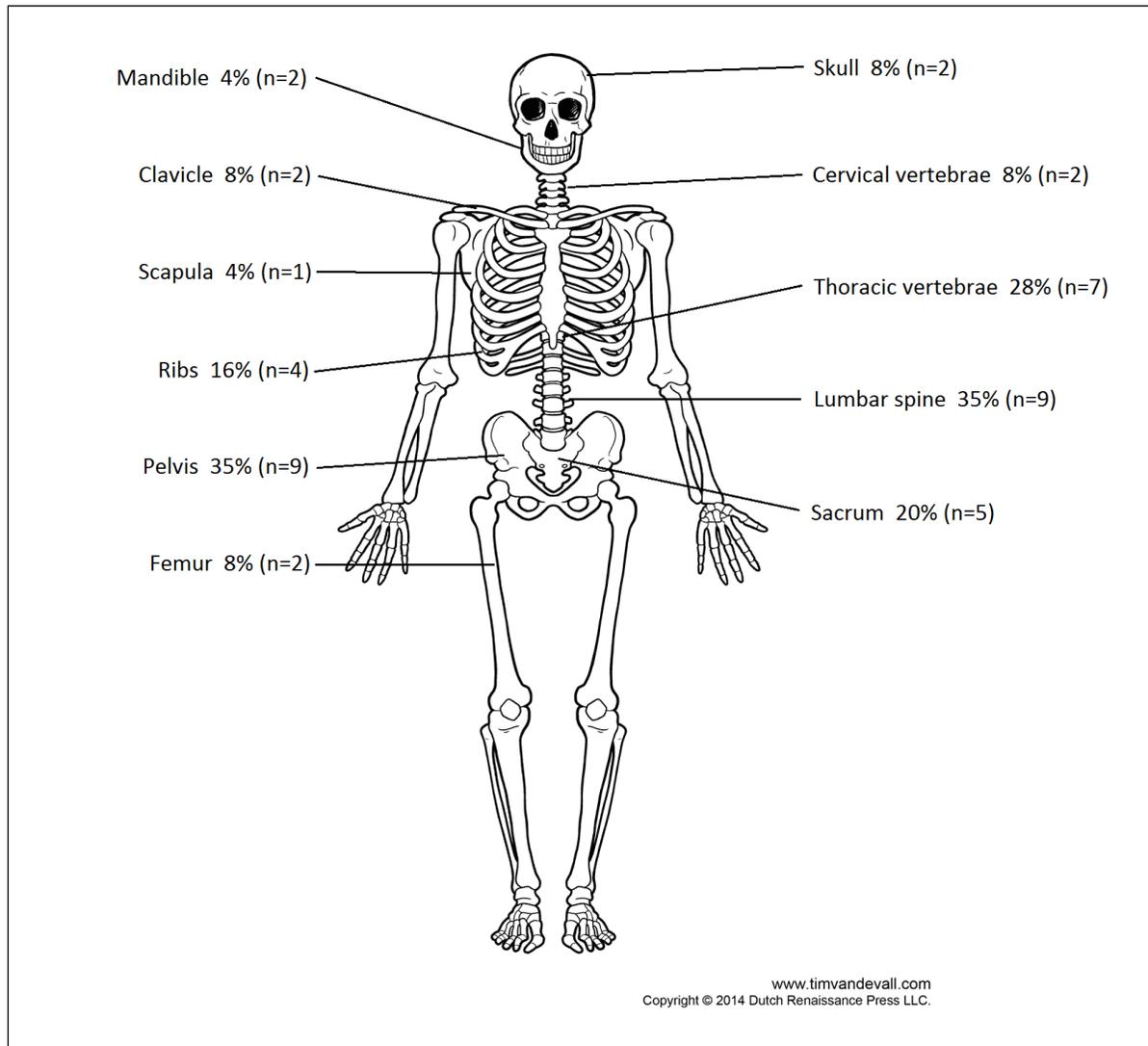
### Symptoms and sites of disease

Pain was the main complaint in 24 out of 25 patients with bone involvement. In addition, 4 women had neurological symptoms, including lower limb weakness and urinary retention due to spinal cord compression. One patient was found to have a clavicular metastasis on PET scan and had no symptoms of bone pain.

The sites of bony involvement were most commonly the pelvic bones (n=9) and lumbar spine (n=9). The thoracic spine (n=7), sacrum (n=5) and ribs (n=4) were the next common sites. Metastases were also found in the cervical spine (n=2), skull (n=2), clavicle (n=2), scapula (n=1) and mandible (n=1). Thirteen patients had multiple bone metastases. The distribution of sites is shown in Figure 1.

With regard to imaging modalities, 4 patients were diagnosed with bone involvement on plain x-ray and 1 on bone scan. Nine women had bone metastases found on PET scan, 6 on CT and 5 on MRI.

Figure 1. The distribution of bone metastases



All 3 patients with neuroendocrine cervical tumours had bony involvement and extraskeletal metastases at cervical cancer diagnosis. Glassy cell type squamous carcinoma was diagnosed on one biopsy and this patient also presented with bony involvement and extraskeletal metastases. The histology of the tumour in the remaining 21 patients was a moderately to poorly differentiated squamous cell cervical carcinoma.

Table 3. Characteristics of patients with bone involvement at primary diagnosis

Patient	Age	Clinical stage at diagnosis	Histological type	Site of bone met	Other mets	Imaging modality	Therapy received	Survival after bone met diagnosis (days)	Survival from cancer diagnosis (days)
1	49	IVb	SCC	Ilium, pubic ramus sacrum acetabulum	LN	X-ray	RT 10 Gy 1#	30	30
2	51	IVb	SCC	Thoracic spine	Lung Liver	CT	RT 10 Gy 1#	117	129
3	41	IVb	NET	Pelvis Femur	Lung Liver LN	MRI	RT 10 Gy 1#	39	71
4	29	IVb	SSC	Sacrum	LN	PET	RT 23.4 Gy 13#	86	105
5	27	IV b	NET	Ischium, pubic ramus, Cervical spine, Ribs, Skull	Lung Liver Brain	MRI	RT 8 Gy 1#	53	53
6	61	IV b	Glassy cell	Thoracic spine, R Clavicle	Lung, LN, Bladder	X-ray	Analgesia	39	40
7	34	III b	SCC	L acetabulum	Lung, Liver, LN	PET	RT 10 Gy 1#	167	413
8	51	III b	SCC	L Clavicle	Lung, Liver, LN	PET	Analgesia	50	102
9	62	III b		Lumbar vertebrae	Lung	Bone scan	RT 20 Gy 5#	80	94
10	35	III b	SSC	Sacrum	None	CT	RT 40.05 Gy 15#	158	222
Mean/ Median	44							66.5	98

SCC – Squamous cell carcinoma, NET – neuroendocrine tumour, LN – lymph nodes

Table 4. Characteristics of patients with bone involvement at recurrence

Patient	Age	Clinical stage at diagnosis	Histological type	Site of bone met	Other metastases	Imaging modality	Therapy received	Days from end of primary Rx to relapse	Survival after bone met diagnosis (days)	Survival from cancer diagnosis (days)
11	39	II b	SSC	Ilium, sacrum, thoracic spine, rib	Liver, LN	PET	RT 6Gy 1#	300	331	767
12	57	II b	SCC	Thoracic vertebrae	Lung	CT	RT 8 Gy 1#	319	36	484
13	25	III b	SCC	R acetabulum	Lung, LN	PET	Analgesia	171	115	419
14	63	III b	SCC	Sacrum, Lumbar spine	Lung, Liver, LN	CT	Analgesia	406	86	645
15	50	II b	SCC	Thoracic spine, Lumbar spine	Lung, pelvis	MRI	RT 8 Gy 1#	436	6	540
16	60	III b	SCC	Cervical spine, Thoracic spine, Lumbar spine	Lung, LN	MRI	RT 20 Gy 5#	63	72	274
17	45	II b	SCC	Ilium	Lung, LN	PET	RT 15 Gy 5#	299	286	664
18	56	III b	SCC	Lumbar spine	None	X-ray	Analgesia	286	78	461
19	35	II b	NET	Lumbar spine, skull	LN	PET	RT 8 Gy 1#	88	32	287
20	55	III b	SCC	Cervical spine, thoracic spine, ribs, scapula, mandible	Lung, LN	PET	RT 12 Gy 3#	203	71	379
21	54	III b	SCC	Acetabulum, rib	Pelvis, LN	PET	RT 15 Gy 5#	369	76	535
22	42	III b	SCC	Ilium	Bladder, LN	MRI	Analgesia	145	85	316
23	49	IV b	SCC	Lumbar spine	Lung, Liver, LN, ovaries	CT	Analgesia	3	138	353
24	41	III b	SSC	Lumbar spine	None	X-ray	RT 20 Gy 5#	113	168	435
25	39	II b	SSC	Lumbar spine	LN	CT	Chemo	427	245	769
Median /mean	47.3							286	85	461

At the time of diagnosis of bony involvement only 3 patients had no other metastases. The other 22 patients all had metastases in multiple organs on imaging including lung (n=15); lymph nodes (n=18), liver (n=7); brain (n=1); bladder (n=2) and local recurrence in the pelvis (n=3).

#### Timeline

In those patients who had bony involvement at cancer recurrence, the time from presentation at the oncology clinic to the time of diagnosis of bone metastases was a median of 366 days (136 – 520 days). The time from the end of primary treatment to the diagnosis of bone involvement was a median of 286 days (3-436).

In all patients the time from diagnosis of bone involvement to death was a median of 80 days (6-331 days). Patients with bone involvement at cervical cancer diagnosis survived for a median of 66.5 days (30-167 days) and patients with bone involvement at recurrence survived for a median of 85 days (6-331 days) after bone involvement was diagnosed. Although survival was shorter in those with bone involvement at diagnosis the means were not significantly different ( $p=0.242$ ).

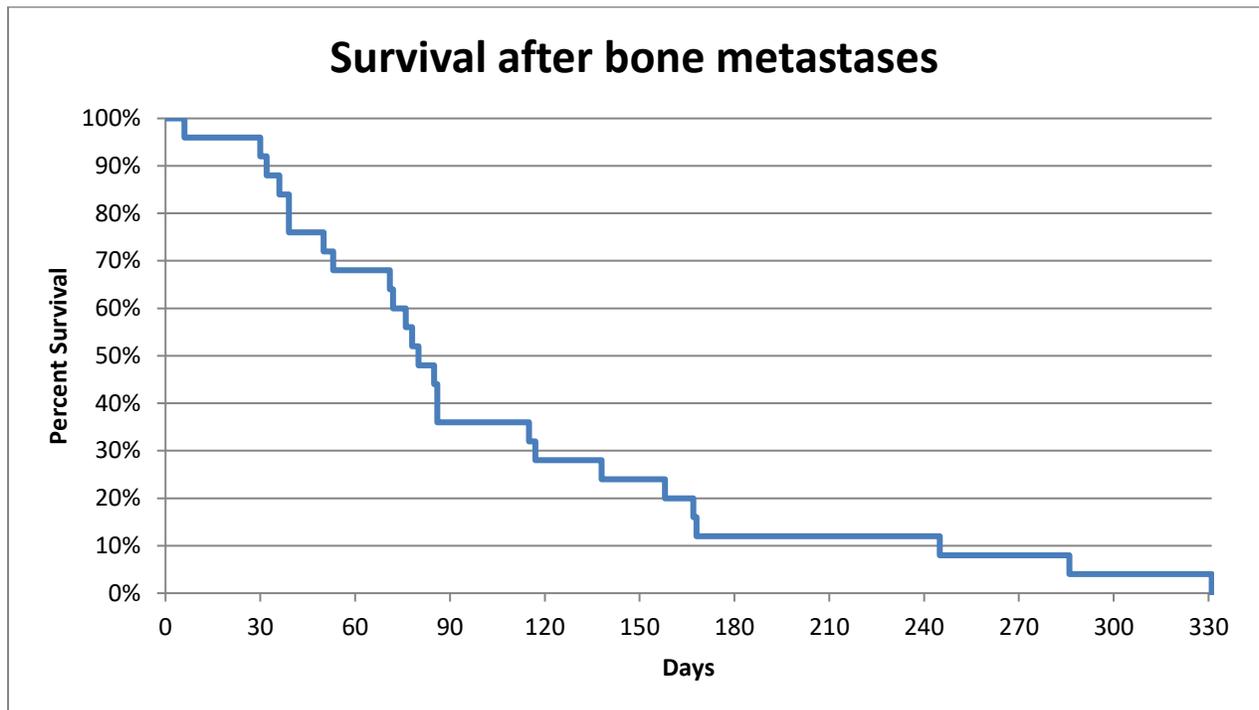
Sixteen patients (64%) died within 3 months of diagnosis of bone involvement and 22 women (88%) died within 6 months. All patients had demised by 11 months after the diagnosis of bone involvement. The survival curve is shown in Figure 2.

#### Risk factors

Twelve patients had a single bone metastasis and survived for a median of 126.5 days (36-286 days) after diagnosis of the bone involvement. Multiple bone metastases were identified in 13 patients with a median survival of 71 days (6-331 days). A comparison of means was not statistically significant, however trended towards better survival in the patients with single bone metastasis ( $p=0.094$ ).

Extraskkeletal metastases were found in 22 patients with a median survival of 78 days (6-331 days). Three patients had no extraskkeletal metastases with a median survival of 158 days (78-168 days). The means were not significantly different ( $p=0.52$ ).

Figure 2. Kaplan-Meier Survival after the diagnosis of bone metastases



WHO performance status was documented in 17 patients. Eight women had a performance status of 1-2 with a median survival of 148 days (39-286). Nine women had a performance status of 3 or 4 with a median survival of 72 days (6-168 days). The T-test for comparison of means was statistically significantly different ( $p=0.024$ ).

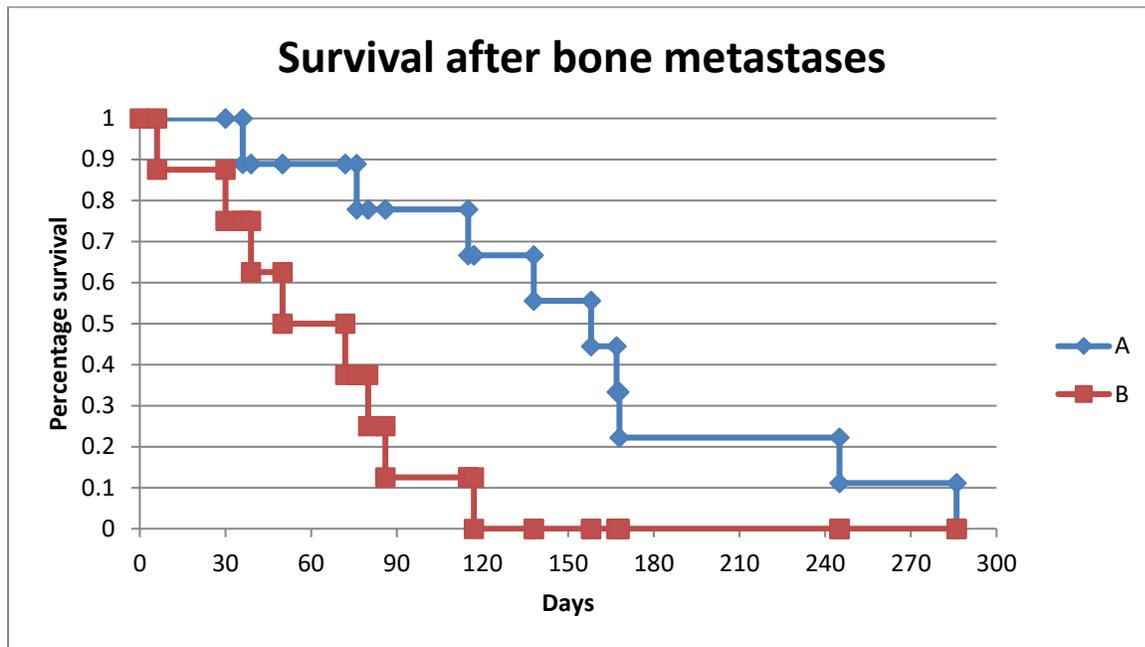
Nine patients with recurrence had a bone metastases-free interval of more than 6 months after the end of primary cervical cancer treatment with a median survival after diagnosis of bone recurrence of 78 days (6-331 days). In 6 patients the bone metastases-free interval was less than 6 months with a median survival of 100 days (32-168 days) which was not significantly different ( $p=0.529$ ). Table 5 shows the comparison of means for the different prognostic parameters.

Table 5. Prognostic risk factors for survival after the diagnosis of bone involvement.

Risk factor	Number of patients (n)	Median survival in days (range)		Comparison of means
Primary bone metastases	10	66.5 days	(30-167)	p=0.242
Metastases at recurrence	15	85 days	(6-331)	
Multiple bone metastases	13	71 days	(6-331)	P=0.094
Single bone metastasis	12	126.5 days	(36-286)	
Extraskkeletal metastases	22	78 days	(6-331)	P=0.52
No extraskkeletal metastases	3	158 days	(78-168)	
Performance status 1-2	8	148 days	(39-286)	P= 0.024
Performance status 3-4	9	72 days	(6-168)	
<6 months after treatment	6	100 days	(32-168)	P= 0.529
>6 months after treatment	9	78 days	(6-331)	
Prognostic score 1-2	9	158 days	(36-286)	P=0.0065
Prognostic score 3-4	8	61 days	(6-117)	

A scoring system with 1 point given for each of primary bone involvement at diagnosis; multiple bone metastases; extraskkeletal metastases and performance status 3 or 4 was assigned for the 17 patients with all these parameters documented. Nine patients had a score of 1-2 with a median survival of 158 days (36-286 days) and 8 patients had a score of 3-4 with a median survival of 61 days (6-117 days). Survival was significantly better for those with a low score ( $p=0.0065$ ). The survival curve demonstrating this significance in survival is shown in Fig. 3. The p-value for the log-rank test = 0.0072 again confirming that these survival curves are significantly different.

Figure 3. Kaplan Meier survival curves comparing prognostic scores



A: Prognostic score 1-2

B: Prognostic score 3-4

Scores according to Matsumiya et al. [4]

### Treatment

Seventeen patients received radiation therapy for bone involvement. Of these, 9 patients received a single fraction with a dose ranging from 6 Gray to 10 Gray, with most receiving a dose of 8 Gray. Two patients received 3 fractions with 4-5 Gray per fraction (12-15 Gray in total). Four patients received 5 fractions with a total dose of 15-20 Gray. Three of these patients had spinal metastases with neurological deficit and one had a recurrence in the external iliac nodes with infiltration of the iliac bone and a good performance status. One patient received chemotherapy for an in-field recurrence. Two patients, who had bone involvement involving the sacrum at cancer diagnosis, received higher doses of radiation in an attempt to treat both the primary disease and the bone involvement. One patient received high dose palliative radiotherapy of 40.05 Gray in 15 fractions. The other patient died before completion of radiotherapy after receiving 23 Gray to the pelvis and sacrum. Five patients received only analgesics, most of whom had multiple other extraskelatal metastases. Two patients did not attend for

treatment of bone metastases. There was no difference in mean survival between those that received radiation therapy for bone involvement and those that did not ( $p=0.544$ ).

Of the 15 patients with bone involvement at recurrence, 6 patients had received radical chemoradiotherapy for their primary tumours. This entailed 46 Gray (FIGO Stage II disease) and 50.4 Gray (FIGO stage III) with weekly Cis-platinum ( $40\text{mg}/\text{m}^2$ ) for 4 to 5 cycles. A further 6 patients had received 46 – 50.4 Gray but with only 1 or no cycles of Cis-platinum, usually due to renal impairment or hydronephrosis. There was no significant difference in the time from end of primary treatment to the development of bone metastases in these 2 groups ( $p=0.356$ ). Single bone metastases occurred more often in those patients who received more than 1 cycle of Cis-Platinum (5 out of 6 patients) and 2 of these patients had no extraskkeletal metastases at recurrence. The patients who did not receive Cis-Platinum developed more multiple skeletal metastases (4 out of 6 patients) and all had more than one extraskkeletal metastasis at recurrence. One patient with a Neuroendocrine tumour received chemotherapy as primary cervical cancer treatment. Two patients with extensive disease received only 10 Gray as a single fraction for palliation of their primary tumour with chemotherapy for extra-pelvic disease.

## **Discussion**

### Prevalence

In this study 3.89% of patients diagnosed with cervical cancer developed bone metastases or had direct bony infiltration. Taking into account the dates for inclusion into this study, the minimum follow up time was 745 days (2 years and 14 days) and the maximum follow up time 4 years and 15 days. The longest duration from presentation at the gynaecology oncology clinic to the diagnosis of bone metastases at recurrence was 520 days, with a median of 366 days (136-520 days).

In a study by Ratanatharathorn et al. over a 10 year period, 75% of patients had developed bone metastases within 36 months of cervical cancer diagnosis and 87.9% of patients within 5 years (median 17 months) [3]. In a Japanese study over a 10 year period, 85% of patients with bone metastases were diagnosed within 2 years after completing treatment [28]. The median time from diagnosis of cervical cancer to diagnosis of bone metastases in a study by Thanappapasr et al. was 16 months and by Yoon et al. was 27 months [8,11]. As our study was limited to 4 years it may be that we have only identified

about 80% of patients who will develop bone metastases and this would explain why our prevalence is lower than the reported literature (4.6%). Although not quantified in this study, a high loss to follow up of women with cancer is observed at our unit.

There were fewer patients with bone involvement at diagnosis (1.56%; 10/642 patients), than previously reported at Tygerberg hospital (2.03%) or at Johannesburg General Hospital (4.6%) [5,6]. These are both historical studies published prior to the implementation of routine 10 yearly Papanicolaou smears in South Africa and this could partly be the reason why women in these earlier studies presented with more advanced disease.

#### Symptoms and sites of disease

As in most studies, pain was the most common symptom of bone involvement in 24 out of 25 patients. Four patients also had associated neurological symptoms. Similarly, Thanappapasr et al. reported 37 out of 41 patients with pain as the presenting complaint, and 5 out of 41 women with neurological deficit [8]. In a pooled analysis of over 5500 patients with bone metastases from various cancers, the authors showed that pain and strong opioid use were significantly increased prior to a skeletal-related event such as a pathological fracture or spinal cord compression [29]. It is of importance therefore to monitor analgesic use carefully during follow up visits as a drastic increase may indicate a bone metastases or skeletal-related event.

Over 60% of bone metastases from cervical cancer occur in the spine with the most common site being the lumbar spine (36.4-51.9%). Multiple bone metastases are diagnosed in over 50% of patients [4,11]. The findings in this study are similar with 70% of metastases occurring in the spine, 35% in the lumbar spine and multiple skeletal metastases diagnosed in 52% of patients.

#### Imaging

There was no standard imaging technique used to diagnose bone involvement in this study. All modalities (X-ray, bone scintigraphy, CT scan, MRI and PET/CT) were employed to diagnose skeletal metastases. In 2015 PET/CT radiotherapy planning became routine in our unit for most patients with FIGO stage III cancer, however this did not lead to an increase in diagnosis of bone involvement, once

again supporting the evidence that routine imaging for detection of bone metastases at diagnosis is not warranted or cost effective [6]. PET/CT may be useful, however, to identify patients with lymph node involvement, as these patients are at high risk of bone metastases. Liu et al. showed that extent of lymph node involvement is a significant predictor of future haematogenous bone metastases [17]. Routine imaging is also not recommended in surveillance of patients after treatment of cervical cancer, however in patients with a clinical suspicion of recurrence, PET/CT may be an appropriate tool as it has a high specificity and sensitivity in detecting metastases and recurrent cancer.

At the time of diagnosis of bone involvement only 3 (12%) patients had no extraskkeletal metastases. Co-existing metastases most commonly occurred in the lungs and lymph nodes. Extraskkeletal metastases were similarly common in 92.6% (50/54) of patients as reported by Matsumiya et al., 78% (32/41) reported by Ratanatharathorn et al. and 53.6% (22/41) patients in a study done by Thanappapasr et al. [3,4,8]. The most common sites for extraskkeletal metastases in all studies were lungs, lymph nodes and liver. If a skeletal metastasis is identified at diagnosis or at recurrence it is important to consider further imaging, as more than 50% of patients will have co-existing extraskkeletal metastases.

#### Timeline

Although risk factors such as non-squamous histology, advanced FIGO stage and extent of lymph node involvement have all been linked to the development of bone involvement, the time from cancer diagnosis to bone involvement varies widely. Most recurrences occur within 2 years of cancer diagnosis, however less than 50% are detected at routine follow up visits [9]. Skeletal metastases at recurrence were diagnosed a median of 366 days (136 – 520 days) after diagnosis of cervical cancer and a median of 286 days (3-436) after the end of treatment. This is a shorter time than in other studies: Thanappapasr et al. found a median of 16 months; while Yoon et al. reported a median time to bone involvement of 27 months [8,11]. The follow up time in this study was limited to 4 years and therefore patients with late recurrences were not included, which may increase the median time. In the study by Yoon et al., patients initially staged with Stage I and IIa disease had a median duration of 22 months after cervical cancer diagnosis to development of bone metastases, while patients with advanced stage cervical cancer had a median time of 15 months [11]. There were no patients with FIGO stage I to IIa in this study cohort and therefore the median duration to development of bone involvement of 12 months (366

days) is more comparable to the median of 15 months in patients with advanced disease reported by Yoon et al. [11].

Survival after the diagnosis of bone metastases is short. In this study 88% (22/25) of patients had died by 6 months after the bone involvement had been identified and all patients had demised by 11 months. The patients with bone involvement at diagnosis of cervical cancer had a shorter (though not significantly) survival than those with bone metastases at recurrence. This is not unexpected as these patients all had advanced stage disease at cervical cancer diagnosis. Survival time after bone metastases is consistently short as reported in other studies. Ratanatharathorn et al. reported a median survival of 3.5 months, Matsumiya et al. a median survival of 5 months, Thanappapasr et al. reported a median survival of 7 months and Yoon et al. a median survival of 10 months [3,4,8,11].

Matsumiya et al. identified a number of independent factors which were associated with a poorer survival namely extraskkeletal metastasis; performance status 3 to 4; multiple bone metastases; bone metastasis-free interval of <12 months and onset time at initial presentation, and used these parameters in a prognostic scoring system [4]. When these factors were analysed in our cohort, performance status was the only significant factor. The bone metastasis-free interval < 12 months was not applicable to patients with bone involvement at diagnosis (n=10) and therefore, in order to apply a prognostic score to our whole cohort, this parameter was omitted. A score of 3-4 was predictive of poor prognosis, with a median survival of 61 days, and this was statistically significant when compared to survival of patients with a score of 1-2. Although our cohort was too small to run multivariate analysis for the different factors, this scoring system has previously been validated in a larger study. Its use is valuable in planning treatment, especially in patients presenting with bone involvement at diagnosis where, if a lengthy treatment is planned, patients with a poor prognostic score may demise before completing radiation. It is also important for counselling the patient and family with regard to survival and in arranging a palliative care plan.

## Treatment

Radiotherapy has been shown to be effective in treating bone metastases and palliating bone pain. As in many other studies, a wide range of different radiotherapy protocols were employed. For uncomplicated bone metastases a single fraction of 8 Gray has been shown to be effective and cost efficient [23]. Nine of the patients in this study received a single fraction. Of the other 8 patients that

received more than 1 fraction of radiation treatment, 3 had complicated spinal metastases with neurological fall-out and 2 received treatment for both the primary tumour and the bone involvement simultaneously. The reasons for the multiple fractions in the other 3 patients are unclear.

Although Yoon et al. showed an improvement in survival in patients who were treated with radiotherapy compared to those treated with chemotherapy, this has not been corroborated by other studies [11]. In this study, survival in patients treated with radiotherapy for bone involvement was compared to no treatment and survival was not improved. The numbers in this study were not sufficient to make any conclusions regarding optimal treatment and there was no standardized treatment regime to allow comparison.

The addition of adjuvant chemotherapy, over and above concomitant chemoradiotherapy, in high risk patients has been shown to decrease the risk of distant metastases and prolong survival [30]. The results of a large randomised control trial (Outback Trial) are awaited to corroborate these findings [31]. Adjuvant chemotherapy may be advocated in patients with locally advanced cancer to lower the risk of treatment failure, including bone metastases, at distant sites.

Bisphosphonates have been shown to reduce the incidence of bone metastases and decrease major skeletal-related events such as pathological fractures, especially in women with low levels of sex hormones [25]. These studies have mostly included women with breast cancer who are either post-menopausal or using aromatase inhibitors as an adjuvant. In post-menopausal women, bisphosphonates have shown an improvement in breast cancer survival. As women with advanced stage cervical cancer have been castrated by radiation therapy, it may be beneficial to include bisphosphonates in their therapy to improve bone health and decrease the risk of bone metastases. In those that already have bone involvement, bisphosphonates may decrease bone pain and the incidence of skeletal-related events.

## Conclusions

Although bone metastases are rare, patients with advanced disease, lymph node involvement and non-squamous histology are at higher risk. Most recurrences, including bone metastases, occur in the first 2 years of treatment. Health care providers should be vigilant during follow up to identify symptoms such as persistent pain or increased analgesic use in order to diagnose bone metastases as early as possible.

Standard x-rays are easily accessible for diagnosis, but not very sensitive. If there is a high index of suspicion, an FDG/PET scan may be warranted as this will not only detect bone involvement, but also extra-osseous recurrence. If an x-ray confirms bone involvement, then further imaging should be done as more than 50% of patients will have other organ involvement.

After the diagnosis of bone involvement has been made, performance status should be documented as this was the most predictive parameter of survival in our study. A prognostic score should be calculated to guide further radiotherapy treatment and for counselling of the patient and family. The use of bisphosphonates needs to be considered, however further studies with regard to use in patients with cervical cancer need to be undertaken. Although radiotherapy has not been shown to improve survival, it is very effective in palliating pain from bone infiltration.

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## Abbreviations

CT	Computed Tomography
DMFS	Distant metastases-free survival
FDG-PET/CT	(18F)-2-fluoro-2-deoxyd-glucose Positron Emission Tomography – Computed Tomography
FIGO	International Federation of Gynecology and Obstetrics
Gy	Gray
LN	Lymph node
MRI	Magnetic resonance imaging
NET	Neuroendocrine tumour
SSC	Squamous cell carcinoma
SRE	Skeletal Related Event
WHO	World Health Organisation