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RESEARCH

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

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Introduction: Bony metastases in cervical carcinoma are rare, however autopsy studies indicate that they are underdiagnosed. A retrospective study was undertaken to describe the risk factors and tumour characteristics and estimate the prevalence of bone involvement in women with cervical cancer at a tertiary institution in South Africa.

Methods: A retrospective cohort analysis of women with cervical cancer diagnosed between 2014 and 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 study identified 642 patients with cervical carcinoma, of which 25 (3.89%) were diagnosed with bone involvement. Ten women had bone involvement at diagnosis and 15 women 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 six months. The WHO performance status score at diagnosis was a significant predictor of survival ($p = 0.024$). A prognostic score was utilised and 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. Healthcare workers should be vigilant to increased analgesic use and chronic pain as these may indicate bone involvement. As survival is short, a prognostic score is valuable in tailoring treatment. A patient's quality of life may be greatly improved by an appropriate radiotherapy and palliative care plan.

Introduction

Cervical cancer is the second 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 recognise as palliative radiotherapy treatment can then be timeously employed to relieve pain and improve quality of life. As survival after the diagnosis of bone involvement is short, an appropriate palliative care plan should be tailored according to the patients' limited prognosis.

The prevalence of bone metastases ranges from 1.8–6.6% (average 4.6%) in a review including 4 422 patients.[3] Two South African studies – the first of radiographic findings on 1 347 women at cervical cancer diagnosis at Johannesburg General Hospital and the second, at Tygerberg Hospital, investigating the detection of bone metastases by bone scan in 540 patients – gave prevalences of bony involvement at diagnosis of 4.6% and 2.03% respectively.[4,5] A higher rate of bone involvement was reported at an autopsy study in all gynaecological cancers.[6] 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.

The risk of developing distant metastases after chemoradiation for cervical cancer was investigated by Schmid et al.[7] The most important factors were lymph node involvement and International Federation of Gynecology and Obstetrics (FIGO) stage of disease. Eleven percent of patients staged Ib to IIIa with negative nodes developed distant metastases, while 38% of patients stage IIIb to IVa or with positive nodes developed distant metastases. In the group with positive nodes, the number of chemotherapy cycles given during radiation was also related to the risk for developing distant metastases.[7] Poorly differentiated tumours and histological types other than squamous carcinoma, such as neuroendocrine, clear cell and adenoid cystic carcinoma, were found to have a greater tendency to spread to bone in a retrospective study.[3]

Matsumiya et al. investigated factors which influence survival after the detection of bone metastases from cervical cancer. After multivariate analysis, five factors proved to be significant: synchronous extraskeletal metastasis; World Health Organization (WHO) performance status; 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 five factors to develop a prognostic scoring system, where one point was allocated for each significant factor. The six-month survival in patients with a score of two was 61.4%. For those with a score ≥ 4, the six-month survival was 12.5% and the median survival was 13 weeks.[8] This information is very helpful in planning treatment, especially when it comes to spinal surgery

for bone metastasis, where a three to six-month life expectancy is a prerequisite.

Radiotherapy has been shown to be an effective palliative treatment for bone pain due to metastatic cancer.[9] A Cochrane review included 3 435 patients and investigated the efficacy of single fraction radiotherapy in comparison to multiple fraction radiotherapy for relieving bone pain. Complete pain relief was reported in one third of patients, with partial relief in 60% of patients, with no difference in efficacy between single fraction and multiple fraction regimens.[10]

Life expectancy after the development of bone metastases from cervical cancer is short, with 95% of patients dying within two 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 aimed to study patients with bone metastases from cervical cancer at Tygerberg Hospital Gynaecological Oncology Unit in order to identify common risk factors and tailor a more suitable follow-up schedule for those who are at high risk.

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 confirming bone metastases.

Patients were initially clinically staged, with basic imaging including chest x-ray, abdominal ultrasound and a cystoscopy. A CT scan was used for planning radiotherapy fields. The standard protocol of 45–50 Gy to the pelvis with concomitant weekly Cis-platinum, followed by 25 Gy given as brachytherapy, was offered to patients who were treated with curative intent. This protocol was modified for patients treated with palliative intent. Follow-up consisted of a clinical examination, and specific investigations based on the patient's symptoms, every three months for the first two years, six-monthly for the next three 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) 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.

Results

642 newly diagnosed cervical cancer patients attended the Gynaecological Oncology Unit between 1 January 2014 and 31 December 2015. Twenty-five 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; range 25 to 63 yr). Six women were found to have bone involvement at initial staging and four women at imaging during radiotherapy treatment planning. The remaining 15 patients had bone metastases at recurrence. Their clinical details are found in Tables I and II.

Pain was the main complaint in 24 out of 25 patients with bone involvement. In addition, four 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 FDG-PET scan and was asymptomatic. The commonest sites of bony involvement were the pelvic bones (n = 9), lumbar spine (n = 9), thoracic spine (n = 7), sacrum (n = 5) and ribs (n = 4). Thirteen patients had multiple bone metastases. The distribution of sites is shown in Figure 1.

All three patients with neuroendocrine cervical tumours and one patient with glassy cell type squamous carcinoma had bony involvement and extraskeletal metastases at cervical cancer diagnosis. The histology of the tumour in the remaining 21 patients was a moderately to poorly differentiated squamous cell cervical carcinoma.

With regard to imaging modalities, four patients were diagnosed with bone involvement on plain x-ray and one on bone scan. Nine women had bone metastases found on FDG-PET scan, six on CT and five on MRI. At the time of diagnosis of bony involvement, only three patients had no other metastases. The

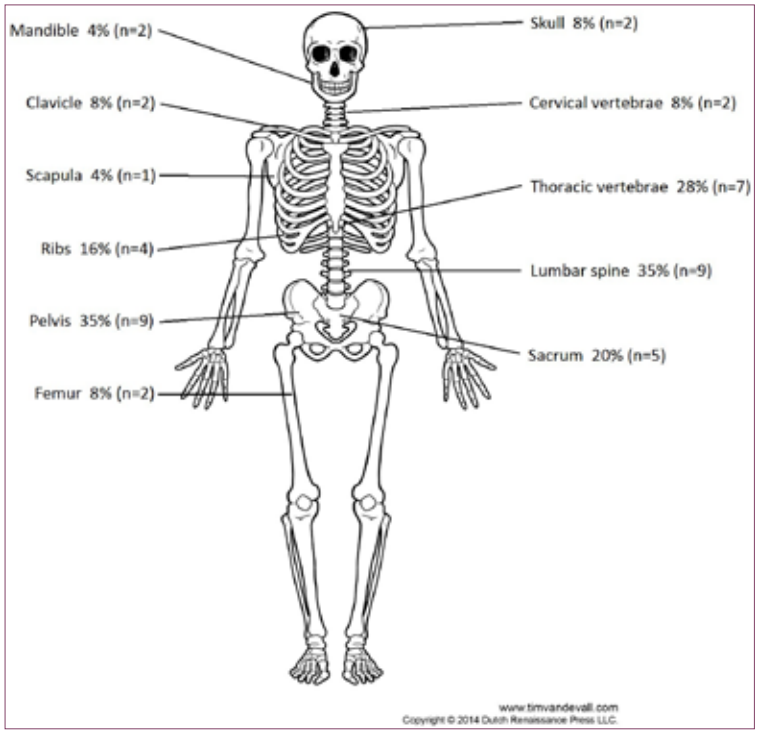


Figure 1. The distribution of bone metastases

Table I. 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 II. 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

other 22 patients all had metastases in multiple organs 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).

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 three months of diagnosis of bone involvement and 22 women (88%) died within six months. All patients had demised by 11 months. The survival curve is shown in Figure 2.

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).

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

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 six months after the end of primary cervical cancer treatment with a median survival after recurrence of

Table III. 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)	
Extraskeletal metastases	22	78 days	(6–331)	P = 0.52
No extraskeletal 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)	

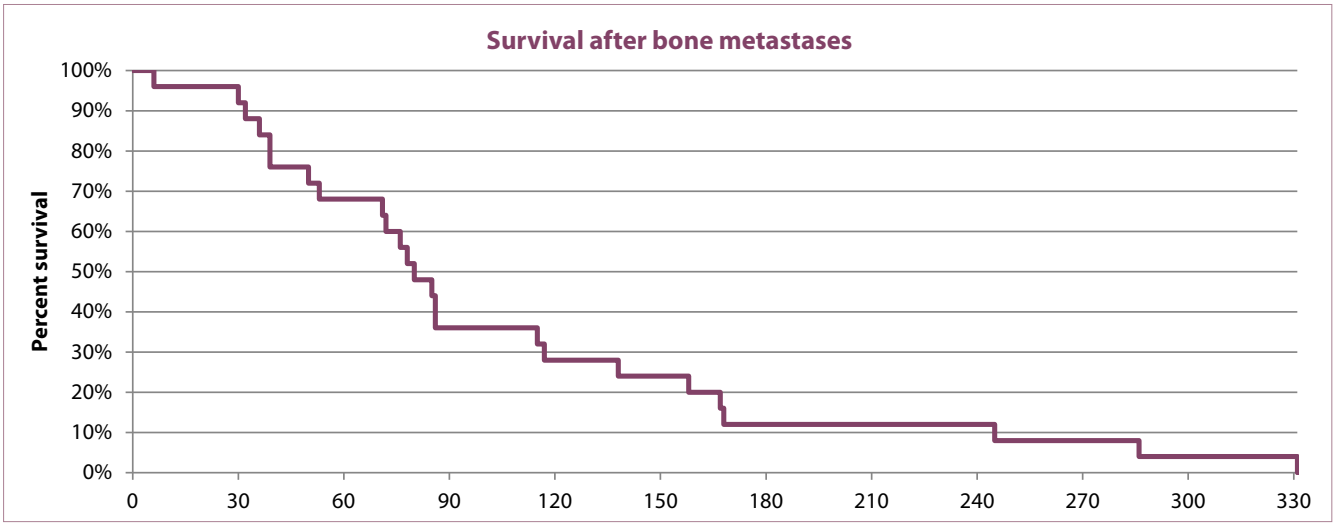
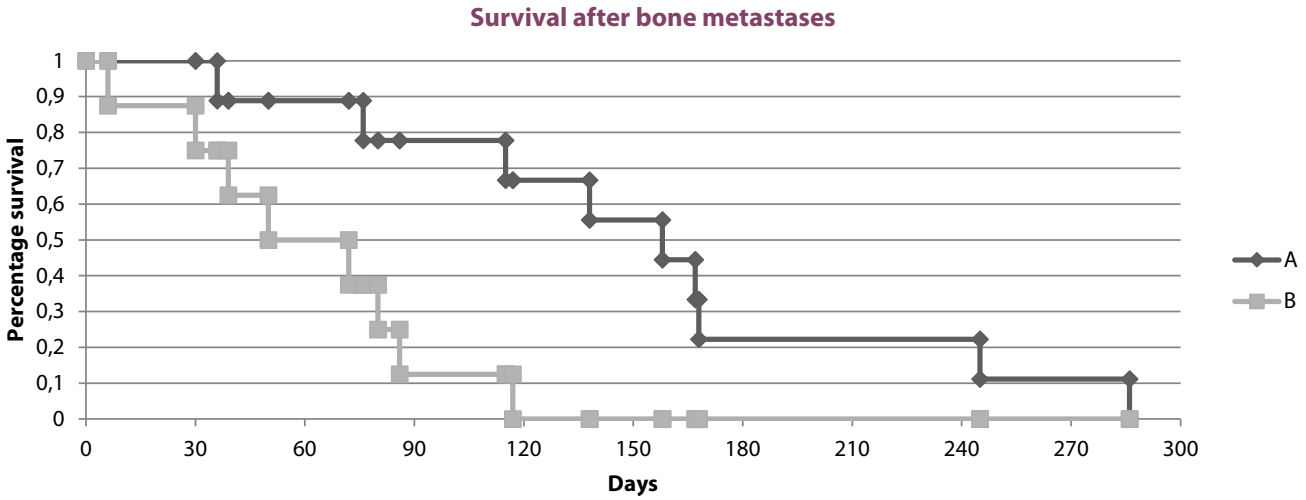


Figure 2. Kaplan-Meier Survival after the diagnosis of bone metastases



A: Prognostic score 1–2. B: Prognostic score 3–4. Scores according to Matsumiya et al. [8]

Figure 3. Kaplan Meier survival curves comparing prognostic scores

78 days (6–331 days). In six patients the bone metastases-free interval was less than six months with a median survival of 100 days (32–168 days) which was not significantly different ($p = 0.529$). Table III shows the comparison of means for the different prognostic parameters.

A scoring system with one point given for each primary bone involvement at diagnosis; multiple bone metastases; extraskeletal 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 eight 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 Figure 3. The p-value for the log-rank test = 0.0072 again confirming that these survival curves are significantly different.

Seventeen patients received radiation therapy for bone involvement. Of these, nine patients received a single fraction with a dose ranging from 6 Gy to 10 Gy, with most receiving 8 Gy. Six patients received 3–5 fractions (12–20 Gy in total). 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. Two patients, who had sacral involvement at cancer diagnosis, received higher doses of radiation to treat both the primary disease and the bone involvement. One patient received chemotherapy for an in-field recurrence. Five patients received only analgesics, most of whom had multiple extraskeletal metastases. Two patients did not attend for treatment of bone metastases. There was no difference in mean survival between those that received radiation therapy and those that did not ($p = 0.544$).

Of the 15 patients with bone involvement at recurrence, six patients had received radical radiotherapy (46–50 Gy) for their primary tumours with 4–5 cycles of concomitant weekly Cis-platinum (40 mg/m^2). A further six patients received radiotherapy, but with only one or no cycles of Cis-platinum, due to renal impairment. There was no significant difference in the time from end of primary treatment to the development of bone metastases in these two groups ($p = 0.356$). The patients who did not receive Cis-Platinum developed more multiple skeletal metastases (four out of six patients) and all had extraskeletal metastases at recurrence.

Discussion

In this study 3.89% of patients diagnosed with cervical cancer developed bone metastases or had direct bony infiltration. The median time from presentation with cervical cancer to the diagnosis of bone metastases at recurrence was 366 days (136–520 days). In a study by Ratanatharathorn et al., 75% of patients had developed bone metastases within 36 months of cervical cancer diagnosis and 87.9% of patients within five years.[3] In a Japanese study, 85% of patients with bone metastases were diagnosed within two years after completing treatment.[11] The median time from diagnosis of cervical cancer to diagnosis of bone metastases in a study by Thanapprapasr et al. was 16 months and by Yoon et al. was 27 months.[12,13] As our follow-up time was limited to four 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%).[4,5] 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.

As in most studies, pain was the most common symptom of bone involvement in 24 out of 25 patients. Four patients had associated neurological symptoms. Similarly, Thanapprapasr et al. reported 37 out 41 patients with pain as the presenting complaint, and five out of 41 women with neurological deficit.[12]

In a pooled analysis of over 5 500 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.[14] It is of importance therefore to monitor analgesic use carefully during follow-up visits as an increase may indicate a bone metastases or skeletal-related event.

Over 60% of bone metastases from cervical cancer occur in the spine, most commonly the lumbar spine (36.4–51.9%). Multiple bone metastases are diagnosed in over 50% of patients.[8,13] 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.

At the time of diagnosis of bone involvement only three (12%) patients had no extraskeletal metastases. Co-existing metastases most commonly occurred in the lungs and lymph nodes. Extraskeletal 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 Thanapprapasr et al.[3,8,12] The most common sites for extraskeletal 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 extraskeletal metastases.

Skeletal metastases at recurrence were diagnosed a median of 366 days (12 months) after diagnosis of cervical cancer and a median of 286 days (9.5 months) after the end of treatment. This is a shorter time than in other studies. In the study by Yoon et al., patients with early stage disease had a median of 22 months from cervical cancer diagnosis to development of bone metastases, while patients with advanced stage cervical cancer had a median time of 15 months.[13] There were no patients with early stage cervical cancer in our study cohort which explains the short duration to development of bone involvement. Survival after the diagnosis of bone metastases is short. In this study 88% (22/25) of patients had died by six months after diagnosis of bone involvement and all patients had demised by 11 months. This is consistent with other studies. Ratanatharathorn et al. reported a median survival of 3.5 months, Matsumiya et al. a median survival of five months, Thanapprapasr et al. and Yoon et al. reported a median survival of seven and 10 months respectively.[3,8,12,13]

Matsumiya et al. identified a number of independent factors which were associated with a poorer survival and devised a prognostic scoring system.[8] When these parameters were analysed in our cohort, performance status was the only significant factor. The bone metastasis-free interval < 12 months was not applicable to 10 patients with bone involvement at diagnosis and therefore to apply the prognostic score to our whole cohort, this parameter was omitted. A score of 3–4 was significantly predictive of poor prognosis compared to patients with a score of 1–2 ($p = 0.0065$). 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 regarding survival and in arranging a palliative care plan.

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 two years of treatment. Healthcare 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. 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 regarding use in patients with cervical cancer need to be undertaken. Although radiotherapy has not been shown to improve survival, a single 8 Gy fraction is very effective in palliating pain from bone infiltration.

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