APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
IMPACT FACTOR 2.595

Peer Review File

Article Information: https://dx.doi.org/10.21037/apm-21-3909

Reviewer Comments

The authors conducted a retrospective review of imaging data to investigate the imaging features of spinal metastases that predict the development of neurological deficits. They included patients from a palliative care unit, who were symptomatic or asymptomatic from their spinal metastases. The authors should be applauded for their rigorous work however. The information the authors present is not something novel as the results presented in the study confirm the understanding/gut feeling of many clinicians. Despite that I do believe that this paper is interesting enough for publication. However, I believe the manuscript is not suitable for publication in its current form. I have the following comments/suggestions/questions:

1. Introduction

Comment 1- please provide references for "radiation therapy after the onset of motor paralysis .... demonstrate durable tumor control"

Reply 1:

van Oorschot B, Rades D, Schulze W, Beckmann G, Feyer P. Palliative radiotherapy--new approaches. Semin Oncol. 2011 Jun;38(3):443-9. doi: 10.1053/j.seminoncol.2011.03.015. PMID: 21600376.

Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J Clin Oncol. 1998; 16(4):1613-24. doi: 10.1200/JCO.1998.16.4.1613. PMID: 9552073.

Shulman RM, Meyer JE, Li T, Howell KJ. External beam radiation therapy (EBRT) for asymptomatic bone metastases in patients with solid tumors reduces the risk of skeletal-related events (SREs). Ann Palliat Med. 2019; 8(2):159-167. doi: 10.21037/apm.2018.10.04. Epub 2018 Nov 6. PMID: 30525770.

Changes in the text:

We added these as new references [Ref. 3, 4, and 5]. [Page 7, line 6]

Comment 2- please provide reference for "radiation therapy certainly .... with spinal

metastases"

Reply 2:

Bluemke DA, Fishman EK, Scott WW Jr. Skeletal complications of radiation therapy. Radiographics. 1994; 14(1):111-21. doi: 10.1148/radiographics.14.1.8128043. PMID: 8128043.

Changes in the text:

We added this as a new reference [Ref. 6]. [Page 7, line 7].

Comment 3- The authors state that they would like to identify patients that can benefit from early radiation, but what about early surgery? Do the authors believe that all spinal metastases are amenable for treatment with radiation therapy whenever detected early enough? Do they believe there would be no role for surgery in case of earlier detection?

Reply 3:

No. As surgical therapy is as effective as radiation therapy, descriptions of surgical therapy were added in the text.

Changes in the text:

We changed the descriptions as follows.

"Radiation therapy applied after the onset of severe motor paralysis or central pain development previously showed lower efficacy than when it was applied while the symptoms were mild. Prophylactic radiation therapy for bone metastases has been reported to provide durable tumor control (3) (4) (5). In addition, direct decompressive surgical resection can improve symptoms following spinal cord injury caused by spinal metastasis (6). Thus, early intervention is essential to prevent irreversible neurological disorders associated with spinal metastases.

However, in clinical practice, interventions are typically first considered when patients with spinal metastases present with severe pain and/or motor paralysis. Such delayed application of interventions for spinal metastases may be due to the patients' lack of awareness of their symptoms, as well as the lack of knowledge of the medical staff. Radiation therapy and surgical decompression certainly have considerable benefits for symptom management and tumor control, but they also have some complications. Radiation therapy can cause bone necrosis, which may worsen spinal instability and fragility in patients with spinal metastases (7). Surgical decompression may be linked to severe postoperative complications, such as bleeding, pneumonia, and heart failure, and may demonstrate limited efficacy

in symptom management (8). Therefore, it is unrealistic that every case of spinal metastasis should be treated with radiation therapy and/or decompressive surgery at the time of detection. Thus, there is a need for a means of inferring when and in which patients such interventions are required.

In this study, we explored the imaging characteristics of spinal metastases that may lead to the development of neurological disorders to identify patients with spinal metastases for whom early intervention would have a favorable benefit-to-risk ratio."

[Page 7, line 3-19, Page 8, line 1-6]

Methods

Comment 4:

What was the rational for including only vertebral levels C3 to T10 and excluding the TL and lumbar area? Areas that are known to often cause problems in patients with spinal metastases.

Reply 4:

In the Methods section, we explained the reason for focusing on the spine from C3 to Th10, namely because the configurations of C1 and C2 are quite different from those of the other spinal vertebrae and because below Th10, the spinal cord is not necessarily present and the symptoms of cauda equina syndrome caused by spinal metastasis below Th10 cannot be distinguished from those of pre-existing lumbar spinal canal stenosis and neuropathy, such as chemotherapy-induced peripheral polyneuropathy.

Changes in the text:

"Symptoms of cauda equina syndrome caused by spinal metastases below Th10 are sometimes indistinguishable from those of pre-existing lumbar spinal canal stenosis and neuropathy, such as chemotherapy-induced peripheral polyneuropathy."

[Page 10, line 16-18]

Comment 5- Figure 1 is unclear to me, what does it represent?

Reply 5:

We apologize for the lack of clarity.

We categorized the symptoms into three clinical categories. Some patients had two of three symptoms, and as shown in Fig. 1.

The three circles on the left are the number of patients who had CT images at the

time of symptom onset: 22 had regional nociceptive pain, 28 had neuropathic pain, and 15 had motor paralysis. Two patients had both neuropathic and motor paralyzes.
The three circles on the right are the number of patients who underwent CT before the onset of symptoms. Seven patients had regional nociceptive pain, 11 had neuropathic pain, and nine had motor paralysis. One patient experienced both neuropathic and motor paralysis.

Changes in the text:
We have changed the text in Legend (Figure 1). It is as follows
"Graphical presentation of the numbers of participants at (left) and before (right) the onset of each spinal metastasis symptom.
The three circles on the left are the number of patients who had CT images at the time of symptom onset: 22 had regional nociceptive pain, 28 had neuropathic pain, and 15 had motor paralysis. Two patients had both neuropathic and motor paralyzes. The three circles on the right are the number of patients who underwent CT before the onset of symptoms. Seven patients had regional nociceptive pain, 11 had neuropathic pain, and nine had motor paralysis. One patient experienced both neuropathic and motor paralysis."
[Page 27, line 2-9]

Comment 6: What do the authors mean with the laterality of spinal metastasis do not demonstrate differences in features? Is only half that of the image used?
Reply 6:
We apologize for the lack of clarity.
Symptoms of spinal bone metastases are not characterized by laterality in the spinal bone (i.e., left and right halves) (12). In this study, we inverted the right half of the images and superimposed them on the left half. Therefore, we used both the left and right halves of the information on spinal metastases.

Changes in the text:
We have changed the text in Methods and Legend (Figure 3) as follows:

Methods
"Therefore, we used both the left and right halves of the information on spinal metastases."
[Page 13, line 1-2]

Figure 3

"Differences in the spinal metastases presence ratio between the asymptomatic and each symptomatic group

Symptoms of spinal bone metastases are not characterized by laterality (i.e., left and right halves) (12). In this study, we inverted the right half of the images and superimposed them on the left half. The darker the red color, the higher the spinal metastases presence ratio in symptomatic patients. The darker the blue color, the higher the ratio of asymptomatic patients. Purple circles indicate regions with a P-value of < 0.05 and odds ratio of > 1."

[Page 27, line 17-19, Page 28, line 1-4]

Comment 7- The authors talk about imaging features to be predictive of symptoms yet I believe predictive is a misleading word, it should be associated with as authors don't follow the imaging over time. They only looked in a very small subset of patients before and after onset of symptoms, this can only be regarded as predictive analysis.

Reply 7:

Thank you for pointing this out.

This study is a pilot study using a small number of patients, and future studies should analyze larger patient cohorts to validate the accuracy of the prediction domains.

We have changes the term "predict" to "infer" in the text.

Changes in the text:

They are the yellow marker in the text.

[Page 1, line 1 ; page 4, line 6; page 4, line 10; page 4, line 15; page 5, line 1 ; page 8, line 2 ; page 8, line 5; page 13, line 15; page 14 , line 19; page 16 , line 19 ; page 17, line 3 ; page 17, line 4 ; page 17, line 6; page 17 , line 17 ; page 17, line 17 ; page 18, line 1 ; page 18, line 2; page 18, line 7; page 18, line 15; page 18, line 17; page 19, line 4; page 20, line 12; page 20, line 15; page 20, line 16].

Results

Comment 8- Do the authors mean by at least one metastasis lesion in the region; involvement of at least one block in the grid of that area?

Reply 8:

According to the reviewer's comment 10, suggesting that we should not develop a predictive model before symptom onset because of the limited number of study participants, we deleted these descriptions in the text.

Changes in the text:

***All descriptions of sensitivity and specificity have been removed.**

Comment 9- the authors mention that for local nociceptive pain they focused on Area A and B, what was the rationale behind this?

Reply 9:

According to the reviewer's comment 10, suggesting that we should not develop a predictive model before symptom onset because of the limited number of study participants, we have deleted these descriptions.

Changes in the text:

***All descriptions of sensitivity and specificity have been removed.**

Comment 10- the authors report sensitivity and specificity values that are very far apart from each other which have very low clinical relevance. I think the authors should just focus on describing the different areas of metastatic involvement and associations with the different symptom categories and leave the sensitivity and specificity out of the paper. It does not add anything aside from confusion.

Reply 10:

Thank you for pointing this out.

We should not develop the predictive model before symptom onset because of the limited number of study participants. Therefore, we deleted the descriptions.

Changes in the text:

***All descriptions of sensitivity and specificity have been deleted.**

Comment 11: Did the authors check that the symptoms of neuropathic pain corresponded with the level that was analyzed? e.g. patient with neuropathic pain in C5 distribution had disease around C4 pedicle level? and also did they correlate this with the side (left vs right?)

Reply 11:

Yes. We confirmed that the clinical symptoms corresponded with the analyzed levels and the laterality, by our experienced pain physicians.
We would change the sentence.

Changes in the text:

The clinical symptoms corresponded with the analyzed levels and the laterality, and these were confirmed by experienced pain physicians.
[Page 9, line 9-10]

Discussion

Comment 12- the authors state that all spinal metastases are immediately treated when detected, this is incorrect. The majority of patients with spinal metastases are asymptomatic and do not receive treatment. Please correct this statement.

Reply 12:

Yes, thank you for pointing this out.
We have changed the sentence as follows:

Changes in the text:

"Radiation and possibly spinal surgery for asymptomatic or minimally symptomatic spinal metastases have been shown to significantly reduce the risk of developing such skeletal-related events (5) (19).
As most symptomatic spinal metastases are immediately treated with radiation therapy or decompressive surgery when detected, our findings of inferable regions for local nociceptive pain in patients with spinal metastases may be of little benefit. In the case of imaging findings that may indicate the onset of symptoms, careful monitoring should be performed, and treatment should be initiated as early as possible according to the expansion of the lesion to prevent the onset of serious symptoms."
[Page 18, line 11-19]

Comment 13- Was there any difference between lytic and blastic lesions?

Reply 13:

Yes, significant differences were observed in the symptomatic group, but not in the asymptomatic group. The distribution of osteoblastic and osteolytic lesions has been added to the Methods, Results, and Discussion sections.

Changes in the text: **We added text on the distribution of osteoblastic and osteolytic lesions.**

Methods:

"Bone metastases are classified as osteolytic, osteoblastic, or mixed, according to the primary mechanism of interference with normal bone remodeling. More than 70% of spinal metastases are osteolytic, 8% are osteoblastic, and 21% are mixed (10). We classified our participants into two types (i.e., osteoblastic and osteolytic). Patients with mixed metastases were included in the osteolytic group (Supplementary Table)."

[Page 10, line 4-9]

Results:

"The number of patients and slices with osteolytic lesions were larger than those with osteoblastic lesions. In contrast, osteoblastic lesions were more common in the asymptomatic group and the local nociceptive pain group before onset (Supplementary Table)." [Page 14, line 7-10]

"The osteolytic type was more common in the spinal canal (Supplementary Figure)." [Page 14, line 13-14]

"There were some significant regions between the osteolytic and osteoblastic types at and before the onset of motor paralysis (Supplementary figure). However, these regions were inconsistent throughout the observation period, which could specifically indicate symptom onset." [Page 14, line 16-19]

"The "neuropathic pain" type patients demonstrated the spread of spinal metastases along the pedicle and circumferentially around the spinal canal at and before onset of symptoms (Figure 3). Osteoblastic regions were more commonly observed in these areas (Supplementary Figure) at the onset, but not before the onset of symptoms." [Page 15, line 1-4]

"The osteoblastic regions lesioned into the inter-circumference of the vertebral body at the onset of symptoms. In contrast, the osteolytic regions were observed on the lateral surface of the vertebral body (Supplementary Figure).

In the asymptomatic group, only a few regions demonstrated significant differences between the osteolytic and osteoblastic types (Supplementary Figure)." [Page 15, line 7-11]

Discussion:

"Osteolytic lesions are more common in these regions, and, in general, are more likely to extend outside of the bone and invade the spinal canal." [Page 16, line 9-10]

Comment 14- Did the authors discriminate between bony and soft tissue involvement in the different regions?

Reply 14:

We could not clearly discriminate between bony and soft tissue involvement. Tumors that extended outside the bone successive to bone metastases, as well as those that remained in the bone, were extracted from the images. In addition, local nociceptive pain due to spinal metastases generally includes pain of both bony and soft tissue origin when bone metastases extend outside the bone. In this study, we treated pain as a local nociceptive pain.

Changes in the text:

We added the following text. [Page 20, line 4-6]

"In this case, we discuss bone pain; however, soft tissue pain may also be included because some tumors extend beyond the bone. There was no significant difference in the local nociceptive pain between the two origins."

Comment 15- Did any of the patients received prior treatment for their metastases?

Reply 15:

No, none of the patients received prior treatment.

Changes in the text:

We added the following text. [Page 9, line 7-8]

"Patients with a history of treatment for spinal bone metastases were excluded."