Size of pelvic bone metastasis as a significant prognostic factor for metastatic prostate cancer patients

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Abstract

Background To investigate the potential prognostic value of image analysis of pelvic bone metastasis in newly diagnosed prostate cancer patients. **Methods** Data from 69 patients with both bone scintigraphy and pelvic CT images were selected for this analysis. Open source software (3D Slicer version 4.8.1.) was used for image analysis. Metastatic pelvic bone lesions were manually contoured, and radiomic features were extracted. As risk factors for overall survival (OS) and cause-specific survival (CSS), 105 radiomic features and clinical risk factors including age, initial prostate-specific antigen, Gleason score, TNM stage, lactate dehydrogenase (LDH), hemoglobin (Hb), alkaline phosphatase, extent of disease, visceral metastases, castration-resistant prostate cancer (CRPC), and number of systemic agents including abiraterone, enzalutamide, docetaxel and cabazitaxel which CRPC patients received were assessed by uni- and multivariate analyses. **Results** Median follow-up was 41 months (range, 0-157 months). Three- and 5-year overall survival rates were 66.6% and 37.9%, respectively. Three- and 5-year cause-specific survival rates were 69.4% and 43.5%, respectively. After multivariate analysis, LDH, Hb, and “maximum 2D diameter” defined as maximum tumor size in the axial plane were detected as risk factors for OS. Gleason sum, LDH, and maximum 2D diameter were detected as risk factors for CSS. **Conclusion** Maximum 2D diameter of pelvic bone metastasis was detected as a significant prognostic factor for metastatic prostate cancer patients.

Background

Patients with metastatic prostate cancer who receive systemic treatment survive an average of approximately 5 years¹. This survival has barely changed even in patients treated using current standards of chemotherapy^{2,3}. However, survival in these patients is highly variable depending on the metastatic site and the burden of the metastatic tumor^{2,4}. One of the reported prognostic factors for these patients is extent of disease (EOD), based on the number of bone metastasis counted on bone scintigraphy. Other widely used prognostic factors include categories based on not only the number of bone metastases, but also metastatic site and status of visceral metastasis, as used in the CHAARTED trial³ and STAMPEDE trial². In the current PSA era, the number of metastases in newly diagnosed patients is relatively small⁵ compared to that in the pre-PSA era⁶. According to our preliminary analysis, most metastatic prostate cancer patients had pelvic bone metastasis, and with metastases limited to the pelvic bone in a substantial number. Analysis focused on pelvic bone metastasis might thus be useful for predicting survival in recently diagnosed metastatic prostate cancer patients. This idea motivated the present study investigating the potential prognostic value of image analysis of pelvic bone metastasis.

Methods

This study was approved by the institutional review board of Kitasato University School of Medicine (B17–245). Medical records of 188 prostate cancer patients with positive results from bone scintigraphy diagnosed in our hospital between April 2003 and October 2014 were reviewed. The numbers of patients

with metastasis to pelvic bone, vertebral bone, or other bone were 154 (81.9%), 127 (67.6%), and 120 (63.8%), respectively. Thirty-three patients (17.6%) showed metastasis limited to the pelvic bone.

We therefore focused on pelvic bone metastasis in this study, and data from 69 patients with both bone scintigraphy and pelvic CT images acquired in our hospital within the range of 1 month were selected for this analysis. Patient characteristics are shown in Table 1. Open source software (3D Slicer version 4.8.11 <https://www.slicer.org/>) was used for image analysis. Pelvic CT data were entered into the software and the metastatic lesion was contoured by one radiation oncologist (H. I.) using a segment editor module referring to bone scintigraphy of the same patient. Scalar volume was resampled into a size of 3 mm×3 mm×3 mm. Radiomic features were extracted from contoured images using a radiomics module. As risk factors for overall survival (OS) and cause-specific survival (CSS), 105 radiomic features including shape-based (n = 13), gray-level dependence matrix (n = 14), gray-level co-occurrence matrix (n = 23), first-order statistics (n = 18), gray-level run length matrix (n = 16), gray-level size zone matrix (n = 16), and neighboring gray tone difference matrix (n = 5) were assessed by univariate analysis. Significant variables on univariate analysis were included in the multivariate analysis.

As clinical risk factors for OS and CSS, age, initial PSA, Gleason score, TNM stage, lactate dehydrogenase (LDH), hemoglobin (Hb), alkaline phosphatase (ALP), and EOD visceral metastases, CRPC, and number of systemic agents including abiraterone, enzalutamide, docetaxel and cabazitaxel which CRPC patients received were assessed by univariate analysis. For clinical risk factors, p value <0.05 was considered as significant. For radiomic features, p value <0.00047 was considered to denote statistical significance according to Bonferroni correction for 0.05 decision threshold. Significant radiomic features from multivariate analysis and significant clinical factors from univariate analysis were included in the final multivariate analysis. All univariate and multivariate analysis were done by using Cox proportional hazard models.

Results

Median follow-up time for the 69 patients was 41 months (range, 0–157 months). During follow-up, 43 patients died. Of these, 37 patients died of prostate cancer, and the other patients died of heart failure (n = 1), brain hemorrhage (n = 1), aspiration pneumonia (n = 1), and unknown causes (n = 3). Three and 5-year OS rates were 66.6% and 37.9%, respectively. Three and 5-year CSS rates were 69.4% and 43.5%, respectively.

Table 2 shows the results of uni- and multivariate analyses of radiomic features. Only shape-based features were detected as risk factors for OS, and “maximum 2D diameter”, defined as the largest size of the tumor surface in the axial plane, was detected as a risk factor for OS after multivariate analysis. None of the risk factors for CSS were detected after uni- and multivariate analyses

Tables 3 and 4 show the results of uni- and multivariate analyses of clinical parameters and maximum 2D diameter. LDH, Hb, and maximum 2D diameter were detected as risk factors for OS after multivariate

analysis. Total Gleason score, LDH, and maximum 2D diameter were detected as risk factors for CSS after multivariate analysis, although EOD was not.

Figure 1 shows the relationships between OS time and maximum 2D diameter. A significant relationship was evident between the two parameters.

Discussion

In 1940, Batson et al. reported a very abundant venous plexus around the pelvic bone and vertebrae, as revealed by intravenous injection of contrast material via the dorsal penile vein⁷. This plexus, now called Batson's plexus, suggests that much of the venous flow, and thus prostate cancer cells, from the prostate gland would run to the pelvic bone and vertebrae. Bone is definitely the most common site of distant metastasis from prostate cancer, and reportedly 86% of prostate primary tumors show only bone metastases⁸.

Our study revealed that the size of a pelvic bone metastasis is a significant risk factor for CSS and OS after multivariate analysis that included EOD and other clinical risk factors. A large variation in survival time is seen among metastatic prostate cancer patients, and many of patients with small pelvic bone metastasis experience relatively long survival (Figure 1). These results suggest that we need to take the pelvic bone separately from other sites of bone metastasis. According to Batson's suggestion, pelvic and vertebral bones might represent a direct drainage system for cancer cells, in the manner of the lymph node system for other types of cancer. Local treatment such as radiotherapy rather than systemic chemotherapy might thus benefit patients with small pelvic metastasis.

EOD is one of the standard predictive factors for patients with metastatic prostate cancer. However, the significance of EOD disappeared after multivariate analysis in our study, although maximum size of the pelvic bone metastasis remained as a significant factor. This result suggests that a simple measurement of pelvic bone metastasis might be better than EOD for predicting survival, and is useful in routine practice even in hospitals without bone scintigraphy.

Recent development of image analysis using radiomic software has helped in the acquisition of additional information from traditional imaging modalities such as CT, and this information could be available via freely distributed software such as 3D Slicer. As the value of the 2D diameter seems relatively stable among various images, the robustness of the radiomic feature was not assessed in this study. Intriguingly, among 105 radiomic features, simple measurement of the size of the pelvic bone metastasis was sufficient to predict survival time.

Our study has several limitations that must be considered: 1) the retrospective manner of the data collection might have introduced some biases; and 2) the same examiner contoured metastatic lesions based on CT and bone scintigraphy, and some variability might be introduced if contouring were performed by other examiners. Further prospective assessments are warranted.

Conclusion

Maximum 2D diameter of pelvic bone metastasis was detected as a significant prognostic factor for metastatic prostate cancer patients.

Abbreviations

OS: overall survival; CSS: cause-specific survival; LDH: lactate dehydrogenase; Hb: hemoglobin; CRPC: castration-resistant prostate cancer; EOD: extent of disease; ALP: alkaline phosphatase

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Kitasato University School of Medicine (B17–245). No consent was required as this study used anonymized registry data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable.

Authors' contributions

TH and HI drafted the manuscript. TH, KT, HT, SK, TK, MH, YW and HI participated in the design of the study. TH and HI performed the statistical analysis. MI and TH supervised the study. TH, KT, HT, SK, TK, MH, YW and HI collected medical information about this study.

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Table 1

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

Figures

Figure 1

Relationships between maximum 2D diameter at the pelvic bone metastasis and survival time in patients with newly diagnosed metastatic prostate cancer.

Supplementary Files

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