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Original Article

Morphometrics predicts overall survival in patients with multiple myeloma spine metastasis: A retrospective cohort study

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Abstract

Background: Treatment strategies for spinal metastases for myeloma range from conservative measures (radiation and chemotherapy) to invasive (surgical). Identifying better predictors of overall survival (OS) would help in surgical decision making. Analytic morphometrics has been shown to predict survival in oncologic patients, and our study evaluates whether morphometrics is predictive of survival in patients with multiple myeloma (MM) spinal metastases.

Methods: For this observational retrospective cohort study, we identified 46 patients with MM spinal metastases who had undergone stereotactic body radiation therapy. OS was the primary outcome measure. Morphometric analysis of the psoas muscle was performed using computed tomography scans of the lumbar spine.

Results: OS was statistically correlated with age ($P = 0.025$), tumor burden ($P = 0.023$), and number of levels radiated ($P = 0.029$), but not with gender. Patients in the lowest tertile of average psoas size had significantly shorter survival compared to the highest tertile, hazard ratio (HZ) 6.87 (95% CI = 1.65–28.5, $P = 0.008$). When calculating the psoas size to vertebral body ratio and correlating this measure to OS, the lowest tertile again had significantly shorter OS compared to the highest tertile, HZ 6.87 (95% CI = 1.57–29.89, $P = 0.010$); the middle tertile also showed significantly shorter OS compared to the highest tertile, HZ 5.07 (95% CI = 1.34–19.10, $P = 0.016$). Kaplan–Meier survival curves were used to visually illustrate the differences in survival between different tertiles (Log-rank test $P = 0.006$).

Conclusions: Morphometric analysis successfully predicts long-term survival in patients with MM. More research is needed to validate these results and to see if these methodologies can be applied to other cancer histologies.

Key Words: Frailty index, morphometric analysis, multiple myeloma mortality, oncologic outcomes, spinal metastases

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INTRODUCTION

Multiple myeloma (MM) is a malignancy defined by the clonal proliferation of monoclonal plasma cells producing M-protein and ultimately leads to end organ disease including hypercalcemia, renal insufficiency, anemia, and bone metastases.^[28] Bone metastases are common in MM and occur in approximately 80–90% of all patients throughout the course of the disease.^[10,25] Lesions can cause severe pain, pathological fractures, and spinal cord compression,^[11,47] which in turn decrease quality of life and each individually increase the risk of mortality.^[4,9,44,48,51] A randomized control trial of patients with metastatic spinal cancer with epidural compression showed that the surgical treatment is superior to radiotherapy alone;^[38] the efficacy of surgery has been confirmed independently in the myeloma literature.^[2,13,20,53] Spinal metastasis scoring systems have been developed^[17,30,49,50] due to an increasing focus on the outcomes after metastatic surgery,^[6,7,24,31,41] however, they have consistently underestimated overall survival (OS) in patients with MM.^[1,33,34,53] Consequently, surgical decision making for this population is challenging. Despite surgery improving OS, neurological outcome, and pain control, oncologic spine surgery is resource intensive and has been reported to delay adjuvant chemotherapy and radiotherapy.^[5,19,22,26,27,46] MM patients are also prone to postoperative morbidities, which can potentially annihilate any survival benefit.^[12] Therefore, other objective assessors of fitness for surgery are needed to provide insight into which patients are appropriate candidates for surgical intervention.

A hallmark of human senescence is frailty, which is defined as a “decreased reserve to physiologic stressors.”^[18,42] Frail patients are at an increased risk of postoperative morbidity and mortality;^[8,32] however, objective measurements of frailty are impractical,^[3,35] and thus sarcopenia, defined as the loss of overall muscle mass, has been used as a surrogate measure to successfully predict surgical outcomes,^[15,16,21,39,52] including after spine surgery.^[56] Morphometrics is the study methodology of patient characteristics which can identify the features of sarcopenia, and thus quantify frailty by proxy. Sarcopenic cancer patients have a higher rate of postoperative morbidity as well as lower progression-free survival compared to patients not displaying this feature.^[23,29,37,43] Given that cancer patients constitute a high-risk population, additional tools are required to better inform patients, families, and physicians about the overall expectations of treatment, whether chemotherapy, radiation, surgery, or palliation.

In this study, we applied morphometric analysis of psoas size to predict OS in patients with MM metastases to the spine. We hypothesized that sarcopenic patients, as measured by cross-sectional psoas size area, would have shorter OS.

MATERIALS AND METHODS

This study was approved by our Institutional Review Board (IRB #9813). We accessed a registry of spinal metastases patients for the period from 2002 to 2012 who had undergone stereotactic body radiation therapy (SBRT) at our institution, and among these, we identified all patients who had a primary diagnosis of MM, as described by pathology reports or clinical records. Of these patients, we identified patients with myeloma spine disease that had a computed tomography (CT) imaging scan within 6 months of SBRT, or identified the most recent CT scan after completion of radiation.

Data sources and variables

Electronic medical records of these patients were the primary data source reviewed. Using previously described methodology,^[54,56] morphometric measurements were taken of the psoas muscle at the L4 level. Briefly, a Philips ePACS viewer (Royal Philips, Amsterdam, Netherlands) was used to measure the cross-sectional area (in square centimeters) of each patient’s psoas muscles. It is intuitive that patients who have smaller stature will have objectively smaller musculature, but are not necessarily more frail; to normalize for stature, we also measured the cross-sectional L4 vertebral body area in the same fashion. This methodology was applied to each patient’s most recent CT scan of the spine which included the psoas and was repeated after radiation. The primary outcome measure was OS. Other demographic variables such as age, number of levels affected, and total SBRT target volume were also considered.

Radiation treatment protocols

At our institution, the gross tumor volume, the clinical target volume, and the planning target volume for a given patient are all identical; during SRS treatment planning, no expansion margin was added to the gross tumor, and thus, the gross tumor volume was equal to the planning target volume. Margins were created using T2-weighted magnetic resonance images to delineate the spinal cord 6 mm above and 6 mm below the defined gross tumor volume. The entire affected vertebral body was included in the target volume. All doses were administered in a single fraction. While EBRT is typically used for MM spinal metastases at other institutions, all the patients in our cohort were carefully selected to receive SBRT/SRS. Each patient was discussed in a multidisciplinary spine tumor board attended by radiation oncologists, neurosurgeons, neuroradiologists, and medical oncologists. Recommendations regarding whether a patient was a suitable candidate for spine SRS were made based on consensus opinion.

Statistical analysis

Measurements of the psoas muscle size were divided into tertiles according to the value of the psoas area

encountered. To account for patient stature, the ratio of average psoas size to that patient's vertebral body cross-sectional area at L4 was considered. The rationale here is that the sizes of these two structures should be proportional to each other and independent of patient stature because the psoas originates from the vertebral body; a large and a small person would have a large and small psoas and vertebral body, respectively, but the psoas/vertebral body ratio should be consistent for both patients.^[14,45,54] We considered normalizing stature by body mass index (BMI), but we were limited by patient records. The validity of using psoas to vertebral body ratio has been described previously.^[14,45,54]

Subsequently, gross tumor volume for SBRT reflects the cumulative tumor volume in the spinal column, and thus, serves as a surrogate marker of disease burden; this hypothesis was tested by dividing the measurements of target volumes into quartiles and subsequently calculating the hazards of death within each quartile. We hypothesize that there was a correlation between the hazards of death and increasing tumor volume (i.e., the hazard ratio would increase with increasing tumor volume).

The main outcome of interest was OS, which was measured from the date of the patient's selected CT scan to the date of death or last follow-up. We chose to measure OS from the date of CT scan and not from the date of diagnosis of myeloma or other time point for a number of reasons. Most importantly, sarcopenia is a time dependent process; we have observed that during the course of oncologic disease muscle mass can change, such as when patients are undergoing chemotherapy. Therefore, measuring death from a time point other than the date of CT would be confounding as patient frailty and sarcopenia are not measured accurately at that time point. Moreover, due to the retrospective nature of this study, not many patients will have a CT scan showing the psoas muscle at the time of diagnosis of myeloma or even from the diagnosis of spinal disease. Therefore, to guarantee a consistent point in time and disease as well as a large patient sample, it was most logical to start from the date of the CT scan. The CT scan chosen was either at the time of SBRT or the most recent CT scan on record. Patients who did not have a known date of death were censored to the date of last follow-up. We are unable to determine cause of death for most patients due to incomplete records.

The median OS in days along with the corresponding 95% confidence interval (CI) was computed for all patients, as well as for subsets of interest. Cox proportional hazards regression analyses provided an estimate of the hazard ratios (HRs) of death. Unadjusted HR tested for the likelihood of mortality with any given variable of interest. Multivariate analysis of adjusted HR controlled for clinically relevant predictors of death along

with statistically significant predictors in the univariate analysis. Kaplan–Meier estimates of time to death were categorized by average psoas tertile. The log-rank test was used to assess differences among the three Kaplan–Meier curves (i.e., tertiles). The Kaplan–Meier curves were censored at 2000 days after imaging, which roughly correlates to 5-year mortality. Patients followed beyond 5 years were considered to be without active systemic disease; thus, changes in psoas size secondary to muscle remodeling no longer correlated with psoas measurements at the time of CT scan. All testing was done at a statistical significance level of 0.05. All statistical analyses were performed using STATA (version 13.0, College Station, TX, USA) and Microsoft Excel.

RESULTS

Participants and descriptive data

Of the patients with MM spine disease within our database, we identified 32 patients who had a CT scan showing the psoas muscle within 6 months of SBRT. We took measurements from the most recent and available CT scan of 46 patients. The mean age of the SBRT cohort was 63.2 (SD \pm 1.9) and for most recent CT cohort was 64.8 years (SD \pm 1.5yrs) [Table 1]. The majority of patients in both populations were male and African American. The mean target volume for the SBRT cohort was 87.8 cm³ and 83 cm³ for the most recent CT cohort, with approximately 43% of the patients in both cohorts having single level disease only.

The mean OS and standard deviation for the SBRT cohort of 32 patients was 1659.8 days (range, 196–4577), and for the 46 recent CT patients it was 1018.6 days (range, 1–4577 days). Table 2 lists the median OS from the SBRT CT scan compared to specific patient demographics, with HR for both unadjusted univariate and adjusted multivariate analysis. Table 3 exhibits the same data but for survival from the most recent CT scan. Multivariate analysis adjusted to account for patient age, sex, and target volume revealed no significant associations from the most recent CT but showed that the CT scan from SBRT was associated with age, gender, and number of levels treated.

Table 4 shows OS in relation to psoas size, with multivariate analysis adjusted to account for interactions with patient age, sex, and target volume. For patients whose psoas measurements were taken at the time of SBRT, those in the lowest (smallest) tertile for average psoas size had a significantly shorter OS compared with those in the highest tertile: 1157.1 vs 2262.6 days, HR 4.8 (95% CI = 1.06–21.62, $P = 0.041$). This association was also observed with measurements taken from the most recent CT scan, with survival being 754.6 vs 1592.8 days, HR 6.87 (95% CI = 1.65–28.5, $P = 0.008$). For measurements taken at the time of SBRT, average

Table 1: Demographic and medical information

Variable	CT from SBRT (n=32)	Most recent CT (n=46)
Mean age at CT scan ± standard deviation (range)	63.2 ± 1.9 (40.34-85.82 years)	64.8 ± 1.5 (40.34-85.82 years)
Ethnicity, n (%)		
African American	20 (62.5%)	26 (56.5%)
Caucasian	10 (31.2%)	18 (39.1%)
South Asian	1 (3.1%)	1 (2.1%)
Hispanic	0 (0%)	0 (0%)
Middle Eastern	1 (3.1%)	1 (2.1%)
Female, n (%)	14 (43.7%)	15 (32.6%)
Male, n (%)	18 (56.2%)	31 (67.3%)
Mean target volume (cm ³) ± standard deviation	87.8 ± 11.2	83.0 ± 8.6
Number of levels affected, n (%)		
1	14 (43.7%)	20 (43.4%)
2	8 (25.0%)	12 (26.0%)
3	4 (12.5%)	6 (13.0%)
4+	6 (18.7%)	8 (17.3%)

Table 2: Survival from CT at SBRT and demographic and medical information

Variable	n	Median survival in days (95% CI)	Unadjusted hazard ratios (95% CI)	P	Adjusted hazard ratios (95% CI)	P
Age at CT	32	Increase over 10 years (median age=5 th decade)	2.18 (1.22, 3.88)	0.008	2.25 (1.19, 4.26)	0.012
Male	18	1937.3 ± 267.3	0.69 (0.25, 1.87)	0.473	0.13 (0.03, 0.53)	0.005
Female	14	1303.0 ± 270.2	Ref		Ref	
Target volume (percentile)						
> 25%	8	2084.0 ± 299.9	Ref		Ref	
25%-50%	8	1257.2 ± 235.8	4.44 (0.83, 23.59)	0.080	3.20 (0.42, 24.51)	0.261
50%-75%	8	1431.8 ± 583.0	3.80 (0.69, 20.90)	0.124	7.03 (0.82, 59.89)	0.074
> 75%	8	1866.1 ± 369.8	2.88 (0.55, 14.95)	0.208	1.98 (0.23, 16.83)	0.532
Number of levels						
Single	14	2076.6 ± 321.1	Ref		Ref	
Multiple	18	1335.6 ± 223.2	3.60 (1.14, 11.34)	0.029	9.08 (1.67, 49.15)	0.010

Table 3: Survival from most recent CT and demographic and medical information

Variable	n	Median survival in days (95% CI)	Unadjusted hazard ratios (95% CI)	P	Adjusted hazard ratios (95% CI)	P
Age at CT	46	Increase over 10 years (median age=6 th decade)	1.65 (1.06, 2.56)	0.025	1.49 (0.92, 2.41)	0.101
Male	31	1088.3 ± 188.4	1.26 (0.52, 3.03)	0.601	0.55 (0.19, 1.60)	0.277
Female	15	872.6 ± 275.9	Ref		Ref	Ref
Target volume (percentile)						
> 25%	12	1454.5 ± 301.1	Ref		Ref	
25%-50%	11	909.9 ± 221.0	3.79 (0.96, 14.93)	0.056	3.19 (0.53, 18.98)	0.202
50%-75%	12	918 ± 398.7	3.71 (0.96, 14.30)	0.056	2.39 (0.46, 12.26)	0.293
> 75%	11	761.7 ± 268.3	4.71 (1.24, 17.94)	0.023	3.82 (0.71, 20.34)	0.116
Number of levels						
Single	20	1242.2 ± 280.1	Ref		Ref	
Multiple	26	846.7 ± 166.1	2.64 (1.10, 6.34)	0.029	1.73 (0.62, 4.85)	0.292

psoas size was also predictive of OS when comparing the lowest tertile with the second tertile: 1157.1 vs 1614.4,

HR 6.84 (95% CI = 1.72–27.18, $P = 0.006$). However, average psoas size was not predictive of OS in other

comparisons in both cohorts. Kaplan–Meier survival curves with log-rank tests for average psoas size tertiles for both CT scan times are visualized in Figure 1. Log-rank test reveals a statistically significant difference in survival from CT scan at the time of SBRT ($P = 0.031$), but not from the most recent CT scan ($P = 0.180$).

When calculating the psoas size to vertebral body size ratio [Table 4], the only statistically significant results were found from the most recent CT scan cohort of patients. The lowest tertile again had significantly shorter OS compared to the largest tertile: 466.3 vs 1840 days, HR 6.87 (95% CI = 1.57–28.89, $P = 0.010$). In addition, the middle tertile developed significantly shorter OS (786 days) compared to the highest tertile, HR 5.07 (95% CI = 1.34–19.10, $P = 0.016$). Figure 2 shows Kaplan–Meier survival curves for average psoas size to vertebral body ratio for both CT scan time points. There was a statistically significant difference in OS between both time points ($P < 0.006$, log-rank test). Similar to the analysis with psoas size alone, this was adjusted to account for patient age, sex, and target volume.

DISCUSSION

Our study results show that morphometric analysis of psoas size can be used as a suitable predictor of OS in select patients with metastatic spine disease from MM. This validates our previously published work on the reliability of psoas size in predicting OS in patients with lung cancer metastases to the spine.^[54] Our work also contributes to the emerging literature that morphometrics can be successfully used as a method to obtain surrogate measures to assess a patient’s overall health.^[23,29,37,43,54] Further comprehensive studies are needed to identify the suitability of morphometrics in earlier stages of malignancy, as well as in other histologies.

Limitations

Our study is limited by its retrospective nature and the fact that data were acquired in a single institution. We are also limited by the electronic medical records, which may have intrinsic and hidden bias caused by patient selection for intent to treat. Our patient population also only includes those who were referred to our center and

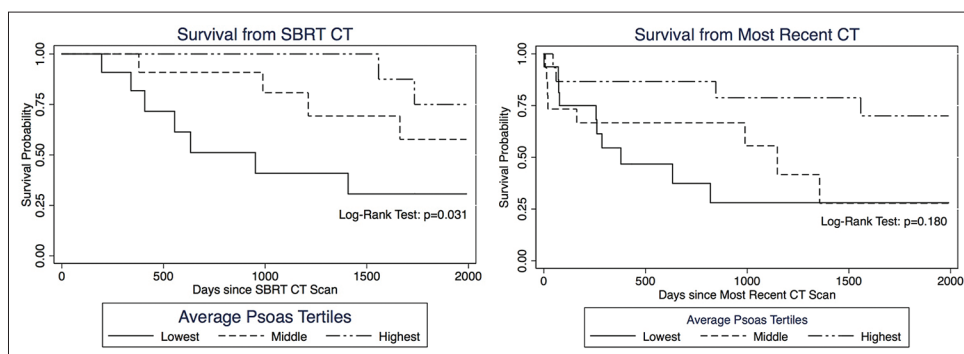


Figure 1: Kaplan–Meier survival curve of average psoas size in tertiles

Table 4: Survival from most recent CT and psoas size. Adjusted hazards ratios controlling for age, and target volume

Variable	CT at SBRT				Most recent CT			
	n	Median survival in days (95% CI)	Adjusted hazard ratios (95% CI)	P	n	Median survival in days (95% CI)	Adjusted hazard ratios (95% CI)	P
Average psoas								
1 st tertile	11	1157.1 (448.4, 1865.9)	4.80 (1.06, 21.62) (1 st vs 3 rd)	0.041 (1 st vs 3 rd)	16	754.6 (217.3, 1292.0)	6.87 (1.65, 28.5) (1 st vs 3 rd)	0.008 (1 st vs 3 rd)
2 nd tertile	11	1614.4 (1017.7, 2211.1)	0.70 (0.15, 3.22) (2 nd vs 3 rd)	0.649 (2 nd vs 3 rd)	15	726.0 (334.0, 1118)	2.10 (0.69, 6.37) (2 nd vs 3 rd)	0.190 (2 nd vs 3 rd)
3 rd tertile	10	2262.6 (1406.5, 3118.6)	6.84 (1.72, 27.18) (1 st vs 2 nd)	0.006 (1 st vs 2 nd)	15	1592.8 (932.6, 2253.1)	1.81 (0.67, 4.84) (1 st vs 2 nd)	0.236 (1 st vs 2 nd)
Ratio of average psoas: Vertebral body area								
1 st tertile	11	1413.6 (454.6, 2372.5)	4.96 (0.96, 25.44) (1 st vs 3 rd)	0.055 (1 st vs 3 rd)	16	466.3 (74.0, 858.5)	6.87 (1.57, 29.89) (1 st vs 3 rd)	0.010 (1 st vs 3 rd)
2 nd tertile	11	1382.0 (1032.3, 1731.6)	2.84 (0.51, 15.71) (2 nd vs 3 rd)	0.230 (2 nd vs 3 rd)	15	786.5 (365.8, 1207.1)	5.07 (1.34, 19.10) (2 nd vs 3 rd)	0.016 (2 nd vs 3 rd)
3 rd tertile	10	2236.2 (1466.4, 3005.9)	1.74 (0.51, 5.94) (1 st vs 2 nd)	0.375 (1 st vs 2 nd)	15	1840.0 (1220.8, 2459.1)	1.35 (0.48, 3.78) (1 st vs 2 nd)	0.564 (1 st vs 2 nd)

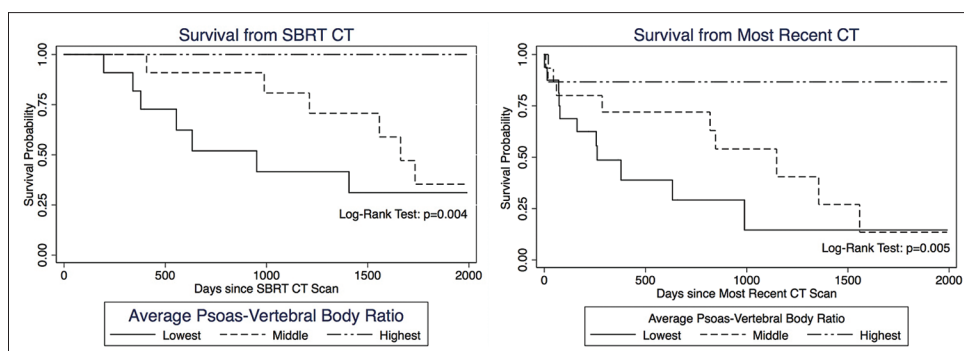


Figure 2: Kaplan–Meier survival curve of average psoas size to vertebral body ratio

also successfully underwent SBRT for their metastatic spinal disease, thereby excluding other patients in earlier stages of disease or those who did not qualify to undergo this specific type of radiation. However, given the standard practice at our institution, we believe that the latter is a small number of patients and that our cohort is representative of the population. We are limited by patient sample size as well. Some of our results approached significance, and during preliminary analysis, we noted that as we increased the size of our patient cohort, our results became significant. Prospective multicenter studies are needed to validate our findings. If they are validated, morphometrics could be used to assist in patient selection surgery and for tailoring specific oncologic treatment regimens.

Interpretation

This study has potential implications for decision making in neurosurgery and oncology. While MM commonly metastasizes to the spine, its current tumor staging system is independent of the extent of osseous involvement;^[28] therefore, patients at various stages of malignancy may have limited or extensive disease burden within the spine.

Spine surgery in this population has been shown to have the potential to improve patient outcomes,^[2,13,20,53] but choosing the appropriate patient to take to surgery remains difficult given how current prognostic scores inaccurately estimate survival.^[1,33,34,53]

Any surgery carries inherent risks, and a postoperative morbidity may debilitate the patient and hasten demise. Therefore, an objective process to assess fitness for surgery and/or longevity is beneficial, as it establishes a basis for therapeutic decision making. Morphometrics is a novel, objective, and comparably simple method to obtain a surrogate measure that allows one to assess an individual's overall health for surgery, as evidenced by its ability to predict outcomes and overall mortality^[23,29,37,43,54] and its association with functional status.^[36,40]

In our study, the use of the psoas size to vertebral body ratio significantly strengthened prognostication. However,

it is intuitive that patients who have smaller stature and therefore objectively smaller musculature are not necessarily more frail. By normalizing the psoas muscle to the size of the vertebral body we could also account for stature and increase the sensitivity of our analysis; the middle tertile being at higher risk for death than the highest tertile ($P = 0.016$), and the log-rank test for the Kaplan–Meier survival curves reached statistical significance ($P = 0.006$). Evidence suggests that the psoas/vertebral body ratio may be more suitable in male patients,^[55] an important fact as our population of myeloma patients is more than two-thirds male. Females are also at a higher risk of being osteopenic and/or having osteoporosis, which may affect the reliability of our vertebral body measurements. Research is warranted to further explore this relationship.

Generalizability

This study is likely generalizable to all patients with MM with metastases to the spinal column. This study population is representative of patients who were referred to radiation treatment of spinal metastases regardless of the decision for surgery, and hence, is not limited by operative plan.

CONCLUSION

Morphometric analysis of psoas size can be used in predicting survival in select patients with MM metastases to the spine. This information can assist in patient selection for surgery, as well as to tailor oncologic treatments.

Disclosures

Ian Lee: Consulting agreement with Medtronic; Honoraria from Varian Medical Systems; Consulting agreement from Monteris.

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Victor Chang: Consulting agreement with DepuySynthes; Consulting agreement with Globus; Research support from Medtronic.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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