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Application of morphometric analysis to patients with lung cancer metastasis to the spine: a clinical study

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OBJECTIVE Predicting the survival rate for patients with cancer is currently performed using the TNM Classification of Malignant Tumors (TNM). Identifying accurate prognostic markers of survival would allow better treatment stratification between more aggressive treatment strategies or palliation. This is especially relevant for patients with spinal metastases, who all have identical TNM staging and whose surgical decision-making is potentially complex. Analytical morphometrics quantifies patient frailty by measuring lean muscle mass and can predict risk for postoperative morbidity after lumbar spine surgery. This study evaluates whether morphometrics can be predictive of survival in patients with spinal metastases.

METHODS Utilizing a retrospective registry of patients with spinal metastases who had undergone stereotactic body radiation therapy, the authors identified patients with primary lung cancer. Morphometric measurements were taken of the psoas muscle using CT of the lumbar spine. Additional morphometrics were taken of the L-4 vertebral body. Patients were stratified into tertiles based on psoas muscle area. The primary outcome measure was overall survival, which was measured from the date of the patient's CT scan to date of death.

RESULTS A total of 168 patients were identified, with 54% male and 54% having multiple-level metastases. The median survival for all patients was 185.5 days (95% confidence interval [CI] 146–228 days). Survival was not associated with age, sex, or the number of levels of metastasis. Patients in the smallest tertile for the left psoas area had significantly shorter survival compared with a combination of the other two tertiles: 139 days versus 222 days, respectively, hazard ratio (HR) 1.47, 95% CI 1.06–2.04, $p = 0.007$. Total psoas tertiles were not predictive of mortality, but patients whose total psoas size was below the median size had significantly shorter survival compared with those greater than the median size: 146 days versus 253.5 days, respectively, HR 1.43, 95% CI 1.05–1.94, $p = 0.025$. To try to differentiate small body habitus from frailty, the ratio of psoas muscle area to vertebral body area was calculated. Total psoas size became predictive of mortality when normalized to vertebral body ratio, with patients in the lowest tertile having significantly shorter survival ($p = 0.017$). Left psoas to vertebral body ratio was also predictive of mortality in patients within the lowest tertile ($p = 0.021$). Right psoas size was not predictive of mortality in any calculations.

CONCLUSIONS In patients with lung cancer metastases to the spine, morphometric analysis of psoas muscle and vertebral body size can be used to identify patients who are at risk for shorter survival. This information should be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens.

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KEY WORDS morphometrics; lung cancer mortality; Stage IV lung cancer; spine complications; frailty index; spinal metastases; spine surgery; morphometric analysis; oncologic outcomes

PATIENT frailty has been defined as a decreased reserve and resistance to stressors, with decline across multiple physiological systems, and is a common end point in human senescence.^{12,43} For a surgeon, the clinical appreciation of a frail patient is important, as a recent

body of literature has shown that frailty can predict morbidity and mortality after general, vascular, transplant, and neurological surgery.^{6,17,28,33,56,57} Unfortunately, measuring human frailty is subjective, burdensome, and impractical in most clinical settings.^{2,33,57} Therefore, surrogate mark-

ABBREVIATIONS CI = confidence interval; HR = hazard ratio; TNM = TNM Classification of Malignant Tumors.

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ers of frailty, namely sarcopenia, have been successfully used to predict postoperative morbidity and mortality following major surgery,^{9,10,17,28,40,46,56} including lumbar spine surgery.⁵⁷ Morphometrics is the measurement of patient attributes that are indicative of sarcopenia and, by extension, frailty.

In terms of oncological surgery, the observation has consistently been that patients who are sarcopenic not only have increased rates of postoperative morbidity and mortality, but also have shorter progression-free survival.^{19,23,37,46} The relationship between increased muscle mass and disease-free survival has even been observed in oncological patients who have not undergone any cancer surgery.^{13,16,24,38,44,50,55} This is a notable observation, as current methodologies for predicting oncological outcomes rely solely on histological grade of the malignancy and its TNM Classification of Malignant Tumors (TNM). Identifying more accurate and specific markers of survival would enable oncologists to discern which patients are appropriate candidates for a particular treatment, be it chemotherapy, radiation, surgery, or palliation.

In this study, we applied morphometric analysis of psoas muscle size to predict oncological outcomes in patients who have had lung cancer metastases to the spine. In our previous work, we identified patients who were at higher risk of postoperative morbidity after lumbar spine surgery by using the psoas area as a marker for sarcopenia.⁵⁷ Our hypothesis is that patients with lung cancer metastasis to the spine will have shorter survival if they have less lean muscle mass as measured by the psoas area.

Methods

Data Acquisition

This study was approved by the Henry Ford Hospital Institutional Review Board. Using a retrospective registry of patients with spinal metastases from 2002 to 2012 who had undergone stereotactic body radiation therapy, we reviewed and identified a population of patients diagnosed with primary lung cancer. This review included all histological subtypes of lung cancer. Additional treatments such as radiation therapy or chemotherapy were inconsistently documented and therefore not included in data acquisition. It should be noted, however, that most patients with lung cancer would have received radiation therapy to the primary site with some form of chemotherapy.

Morphometric Analysis

The full extent of our methodology for morphometric analysis has been described previously.⁵⁷ Briefly, morphometric measurements were taken of the psoas muscle at the L-4 level, and a Philips ePACS viewer was used to measure the circumference (in cm²) of each patient's psoas muscles. In addition, the L-4 vertebral body area was measured and recorded in similar fashion. Measurements were made using the patient's most recent CT scan of the lumbar area. Psoas muscle sizes were divided into tertiles according to total psoas area. Because the psoas measurements were dependent on sex, the tertiles for left, right, and total psoas were computed within the male and female cohorts separately using different cutoff points. In

addition, the ratio of left, right, and total psoas area to the vertebral body area was considered. Tertiles were computed for these new variables using different cutoff points for males and females. Besides the tertile cutoff points, the median cutoff point was also investigated.

In addition to absolute psoas size, we also attempted to normalize psoas size based on each individual patient's stature. Intuitively, patients with smaller stature will tend to have smaller psoas sizes. As a result, these patients would not necessarily be sarcopenic nor at risk for shorter survival. Our method of normalization of psoas muscle size with body habitus consisted of calculating the ratio of psoas muscle area to vertebral body area as a separate variable for morphometric analysis. The primary outcome measure was overall survival, which was measured from the date of the patient's scan to date of death. For patients who were still alive at the time of analysis, survival was calculated to the most recent documented follow-up evaluation.

Statistical Analysis

The median survival in days along with the corresponding 95% confidence interval (CI) was computed for all patients, as well as subsets of interest. Cox proportional hazards regression analyses were done to estimate the hazard ratios (HRs) and test for differences in the variables of interest. All testing was done at the 0.05 level. The statistical program SAS (version 9.4, SAS Institute) was used for data analysis.

Results

There were 168 patients with spinal metastases from lung cancer identified and included in this study. There was 1 person without a right and total psoas measurement because of the location of the tumor. Patient demographics can be found in Table 1. The average age (\pm SD) at the time of CT scan was 65.3 ± 11.3 years, with a range from 33 to 97 years old. Ninety (54%) of the patients were male. There were 78 patients (46%) with single-level metastases and 90 (54%) with multiple-level metastases. There were 24 patients (14.3%) treated surgically in this series, with 6 (3.6%) undergoing instrumentation.

The median survival for all patients was 185.5 days (95% CI 146–228 days). The associations of overall survival with age, sex, and the number of levels were not significant (Table 2). Comparisons of psoas size with survival can be found in Table 3. When considering the total and mean psoas tertiles, no significant differences in survival were detected. However, the difference between patients above and below the median of total psoas size and the median of mean psoas size was significant, with patients below the median having shorter survival (HR 1.43, $p = 0.025$ for total psoas size; HR 1.42, $p = 0.026$ for mean psoas size). The Kaplan-Meier survival curves for this data set provide a visual representation of the differences in survival between these two groups (Fig. 1). Using the left psoas only, patients in the lowest tertile (smallest psoas size) had significantly shorter survival (median 139 days) as compared with the middle (median 164 days, $p = 0.038$) and highest (median 263 days, $p = 0.011$) tertiles. Survival

TABLE 1. Patient demographics

Variable	Value
Age (yrs)	
Mean (SD)	65.3 (11.3)
Median (range)	64 (33–97)
Sex (%)	
Male	90 (54)
Female	78 (46)
Race (%)	
Caucasian	104 (62)
African American	52 (31)
Other	7 (4)
Not available	5 (3)
No. of levels treated (%)	
1	78 (46)
2	55 (33)
3	23 (14)
4	9 (5)
5	2 (1)
6	1 (0.6)
Target volume in ml (%)*	
Mean (SD)	51.7 (39.3)
Median (range)	41.3 (0.565–209)

* In 143 patients.

of the lowest tertile was also significantly decreased when compared with a combination of the other two tertiles, 139 days versus 222 days, respectively ($p = 0.007$). The Kaplan-Meier survival curve for morphometrics based on left psoas size is shown in Fig. 2. No significant differences were detected for the right psoas, using both tertile and median cutoff points.

We also performed a similar analysis using values for psoas size that were normalized for patient size by calculating a ratio of psoas muscle area to vertebral body area (Table 4). When applying this ratio to total psoas size, patients in the lowest tertile had statistically significant shorter survival as compared with the combination of the other two tertiles (HR 1.49, 95% CI 1.07–2.07, $p = 0.017$). This normalization increased the sensitivity of our morphometric analysis, as total psoas size tertiles without normalization to vertebral body size did not show any statistically significant differences in survival (Table 2). The Kaplan-Meier survival curves of total psoas size to vertebral body ratio are shown in Fig. 3. Similar results were found for the ratio of left psoas size to vertebral body size, as patients in the lowest tertile had significantly shorter survival than a combination of the other two tertiles (HR 1.47, 95% CI 1.06–2.04, $p = 0.021$). No significant differences were detected for the ratio of right psoas size to vertebral body size.

Discussion

Since the publication of Patchell et al.’s seminal study on surgical treatment of patients with spinal metastases,³⁹

TABLE 2. Overall survival and patient demographics

Variable	N	Median Days of Survival (95% CI)	HR (95% CI)	p Value
Age		(Increase over 10 yrs)	0.92 (0.79–1.06)	0.234
Sex				
Male	90	188.5 (138–273)	Reference	0.505
Female	78	179.5 (124–222)	1.11 (0.81–1.52)	
No. of levels				
Single	78	183 (132–254)	Reference	0.412
Multiple	90	185.5 (133–230)	1.14 (0.84–1.55)	

there has been an interest in spinal oncology as a subspecialty and subsequently a growing body of literature regarding outcomes on the subject.^{4,5,20,27,42} Surgical decision-making for this population can be challenging. While surgery can improve overall survival and neurological outcome, and provide pain control, these procedures delay cancer treatments (chemotherapy and radiation) and are resource intensive.^{3,14,18,21,22,51} Surgical risk is also high, with postoperative morbidity as high as 76%,⁷ which may diminish any benefit of surgery and hasten patient demise.

Several authors have reported different classification schemes attached to surgical decision-making algorithms to treat the patient with spinal metastasis in general.^{11,26,45,52,53} However, these scoring systems have a limited prognostic capability.^{14,41,49} With continued refinements to surgical technique as well as advances in implant technology, surgeons are able to undertake increasingly ambitious resections followed by complex reconstructions.^{1,25,35} An objective assessment of fitness for surgery would provide insight into which patients are better surgical candidates. There is a recently established and objective scoring system designed specifically to predict functional outcome and survival in surgical patients with lung cancer metastases to the spine;^{29–32} this system uses markers of disease severity (visceral metastases, multiple-level metastases, inability to ambulate, etc.) to predict surgical outcome and survival. Our work differs in several ways. Our work identifies at-risk patients independent of the extent of metastases and in a nonsurgical population, and so it may be applicable in a broader sense. Psoas size, as a surrogate for frailty, has been verified to be predictive of morbidity and mortality after both general^{9,10,17,28,40,46,56} and spine surgery.⁵⁷ While our current results did not focus on morbidity and mortality after oncological surgery, we did show that patients who were sarcopenic, as measured by a morphometric analysis of psoas size, had decreased survival. This morphometric parameter can be applied in conjunction with other classification criteria to help guide surgical decision-making. An observation of small psoas size and risk of shorter survival could be useful in determining if a patient is unfit for surgery.

The use of the vertebral body measurement to successfully normalize body habitus has been performed in trauma patients,⁸ as well as in the assessment of peripheral vascular disease,⁴⁸ with mixed results. Its current application—to predict mortality in oncological patients—is novel. The impetus for finding a way to normalize each

TABLE 3. Overall survival and psoas size*

Variable	N	Median Days of Survival (95% CI)	HR (95% CI)	p Value
Total psoas tertiles				
Lowest	55	157 (107–204)	1.38 (0.94–2.02)	0.10 (1 vs 3)
Middle	57	133 (102–230)	1.28 (0.87–1.88)	0.202 (2 vs 3)
Highest	55	280 (191–356)	1.07 (0.74–1.57)	0.71 (1 vs 2)
Mean psoas tertiles				
Lowest	57	173 (115–204)	1.34 (0.92–1.95)	0.124 (1 vs 3)
Middle	53	127 (101–237)	1.21 (0.83–1.79)	0.323 (2 vs 3)
Highest	58	270.5 (191–337)	1.10 (0.75–1.62)	0.613 (1 vs 2)
Total psoas				
Less than median	84	146 (115–186)	1.43 (1.05–1.94)	0.025
Greater than median	83	253.5 (179–302)	Reference	
Mean psoas				
Less than median	83	146 (115–186)	1.42 (1.04–1.94)	0.026
Greater than median	85	253 (174–302)	Reference	
Lt psoas tertiles				
Lowest	55	139 (91–185)	1.65 (1.12–2.42)	0.011 (1 vs 3)
Middle	57	164 (115–269)	1.10 (0.75–1.61)	0.636 (2 vs 3)
Highest	56	263 (191–337)	1.50 (1.02–2.20)	0.038 (1 vs 2)
Lt psoas†				
Lowest	55	139 (91–185)	1.57 (1.13–2.20)	0.007
Middle & highest	113	222 (164–288)	Reference	
Rt psoas tertiles				
Lowest	55	173 (115–214)	1.39 (0.95–2.03)	0.094 (1 vs 3)
Middle	56	136 (102–211)	1.29 (0.88–1.90)	0.187 (2 vs 3)
Highest	56	276 (191–337)	1.07 (0.73–1.53)	0.723 (1 vs 2)

* Boldface type indicates statistical significance.
 † First tertile versus second and third tertiles.

patient comes from the observation that patients who have a small body habitus may not be sarcopenic, and would be falsely classified as more frail by measuring lean muscle mass alone without normalization. The vertebral body, in a nonpathological state, maintains its size independent of age.³⁴ Because the origin of the psoas muscle size is on the

transverse process of the spine, it is intuitive that a normal psoas muscle size should be in proportion to the size of the vertebral body. Calculating a ratio between psoas size and vertebral body size could provide a more accurate measurement of sarcopenia.

It is important to note that we observed a statistically significant relationship with survival when looking at total

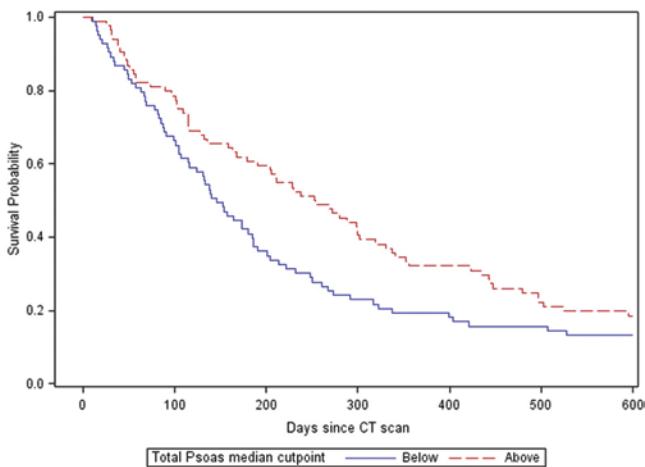


FIG. 1. Kaplan-Meier survival curve of total psoas size using median as the cutoff point.

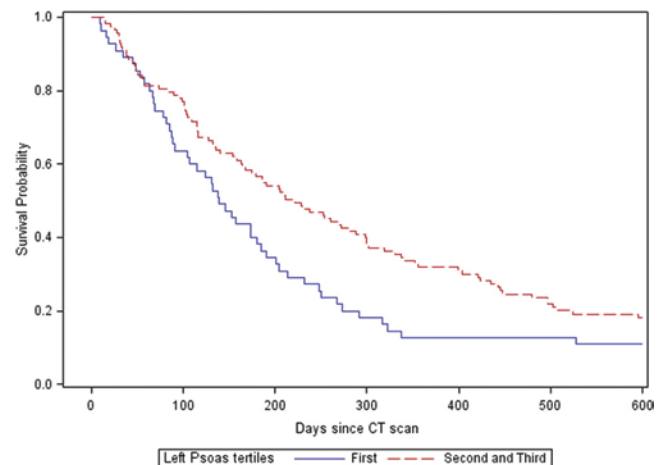


FIG. 2. Kaplan-Meier survival curve of left psoas tertiles.

TABLE 4. Comparison of overall survival and psoas size to vertebral body ratio*

Variable	N	Median Days of Survival (95% CI)	HR (95% CI)	p Value
Ratio of total psoas to vertebral body area†				
Lowest tertile	56	138.5 (83–191)	1.49 (1.07–2.07)	0.017
Middle & highest tertile	111	211 (168–288)	Reference	
Ratio of lt psoas to vertebral body area†				
Lowest tertile	56	135 (85–168)	1.47 (1.06–2.04)	0.021
Middle & highest	112	216.5 (179–280)	Reference	
Ratio of rt psoas to vertebral body area				
Lowest tertile	57	153 (99–214)	1.14 (0.78–1.67)	0.489 (1 vs 3)
Middle tertile	53	191 (133–288)	1.05 (0.72–1.54)	0.798 (2 vs 3)
Highest tertile	57	228 (124–302)	1.09 (0.74–1.68)	0.665 (1 vs 2)

* Boldface type indicates statistical significance.

† First tertile versus second and third tertiles.

psoas size, mean psoas size, and left psoas size, but not for the right psoas. These results were maintained even after internal normalization with vertebral body size. On closer analysis of our previous results predicting morbidity after lumbar spine surgery,⁵⁷ we also found that the right psoas size did not provide statistical significance, but total psoas size, mean psoas size, and left psoas size did. In coordination, these two findings suggest that this observation may be a reflection of reality, whereas the left psoas muscle may be a better indicator of sarcopenia or frailty. To our knowledge, this is the first time that this phenomenon has been identified in the psoas size morphometric literature. We are unable to identify a plausible rationale at this moment, although we hypothesize that left cerebral hemispheric dominance causes attenuation of right-sided sarcopenia due to the more frequent use of that side. Ultimately, further and more comprehensive studies are required to explore this finding to definitively conclude whether this observation is a true reflection of the general population.

Our study illustrates that morphometric analysis of psoas size is predictive of survival in patients with lung cancer metastasis to the spine. These findings have potential applications to oncology as well as neurosurgery. Lung

cancer is common and the leading cause of cancer death in the world.⁵⁴ The 5-year survival rate for patients with lung cancer is poor—only 17% of patients in all stages of the disease—with only a 2% 5-year survival rate for patients with Stage IV cancer.¹⁵ All patients in our cohort had Stage IV lung cancer, given that all had distant metastases to the spine.³⁶ From an oncological perspective, there are treatments available at this stage of lung cancer, but current guidelines recommend basing treatment strategies on a patient’s performance status.⁴⁷ To date there are no studies that directly compare performance status with frailty. However, it has been reported that frail patients may have poor performance status, but a poor performance status does not always indicate frailty.^{12,43} Our results suggest that analytical morphometrics as a measurement of frailty can be predictive of survival in patients with lung cancer. The ultimate utility of this finding, which can only be achieved after further testing and validation, would be to use psoas size to guide oncological treatment by identifying those patients who are better suited for aggressive interventions.

The chief limitation of our study is its retrospective nature. While the electronic medical record is robust, we are unable to account for any hidden bias associated with retrospective studies. Prospective multicenter studies would be necessary to further validate our findings.

Conclusions

Morphometric analysis of psoas size can be used to predict survival in patients with lung cancer metastases to the spine. With further work and validation, this information could be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens. Further research is needed to confirm these results and to see if these methodologies can be applied to other cancer histologies.

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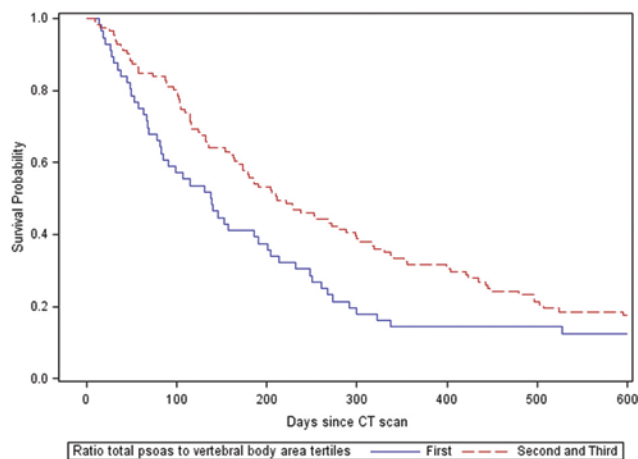


FIG. 3. Kaplan-Meier survival curve of total psoas to vertebral body ratio tertiles.

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Conception and design: Zakaria, Chang, Lee, Siddiqui. Acquisition of data: Zakaria, Chang, Basheer, Boyce-Fappiano, Elibe. Analysis and interpretation of data: Chang, Zakaria, Schultz, Lee. Drafting the article: Zakaria, Chang, Schultz. Critically revising the article: Chang, Zakaria, Basheer, Lee, Siddiqui. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chang. Statistical analysis: Schultz. Study supervision: Chang.

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