Multimodal Imaging Aids in the Diagnosis of Perineural Spread of Prostate Cancer

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BACKGROUND: **The perineural spread of prostate cancer into pelvic peripheral nerves is a rare, but increasingly recognized, entity. This form of metastasis invades the lumbosacral plexus via the splanchnic nerves innervating the prostate. The prevalence of perineural spread is likely underappreciated, and further imaging-based studies are needed to elucidate its true frequency.**

METHODS: **A retrospective review was performed using an institutional radiology database. Medical reports from patients with prostate cancer who had undergone positron emission tomography (PET) imaging were queried for terms suggestive of perineural spread. PET and magnetic resonance imaging (MRI) from the identified patients were blindly reviewed for peripheral nerve involvement by 2 nuclear medicine and 2 musculoskeletal radiologists.**

RESULTS: **A total of 22 patients were identified. After review by the radiologists, 16 patients had positive findings of perineural spread found on PET and 15 had abnormalities found on MRI involving lumbosacral plexus neural elements. All patients with biopsy-proven neoplastic perineural spread (including 1 patient with malignant peripheral nerve sheath tumor) had positive findings on both PET and MRI. All patients with biopsy-proven inflammatory lesions had negative PET and variable MRI findings.**

CONCLUSIONS: **The perineural spread of prostate cancer might be more common than previously thought. The use of multimodal imaging for patients suspected of having perineural spread should be a part of the treatment algorithm. Targeted fascicular biopsy might be indicated for patients with progressive neurological deficit and an unclear diagnosis.**

INTRODUCTION

Prostate cancer is the most common cancer and second most common cause of cancer-related death in the U.S. male population, with increased rates of incidence and mortality seen in the African-American population.[1] The local growth of tumor cells into any of the 3 nerve sheath layers is known as perineural spread. This form of metastasis can affect the lumbosacral plexus and sciatic nerve. Also, although this was initially thought to be a rare entity, its presence is becoming increasingly recognized.[2-7] Neoplastic spread is thought to reach the lumbosacral plexus via retrograde travel through the splanchnic nerves and hypogastric nerves innervating the prostate.[3,5,8] The slow, progressive nature of nerve involvement can often make perineural spread difficult to diagnosis.

In addition to perineural spread, the differential diagnosis of a progressive lumbosacral plexopathy in a patient with a history of pelvic malignancy often includes radiation neuritis, chemotherapy-induced neuropathy, inflammatory neuropathy, new malignancy (e.g., malignant peripheral nerve sheath tumor [MPNST] or lymphoma), and compression neuropathy from an extrinsic malignant mass or lumbar spine disease.[9] These other diagnoses can have different clinical presentations, but the variations are subtle. Further obscuring the diagnosis in patients with a history of prostate cancer, an inconsistent relationship

Key words
- Lumbosacral plexus
- MRI
- Magnetic resonance imaging
- PET
- Perineural spread
- Positron emission tomography
- Prostate cancer
- Sciatic nerve

Abbreviations and Acronyms
CT: Computed Tomography
FDG: Fluoro-2-D-deoxyglucose
MPNST: Malignant peripheral nerve sheath tumor
MRI: Magnetic resonance imaging
PET: Positron emission tomography
PSA: Prostate-specific antigen

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exists between perineural spread and prostate-specific antigen (PSA) levels.[5,9] For example, patients with perineural spread can present with normal PSA values after years of remission.[10]

A critical component of the evaluation for patients with new lumbosacral plexopathy is high-resolution pelvic magnetic resonance imaging (MRI), especially if they have a history of prostate cancer.[8] The MRI findings of perineural spread include an increased T2-weighted signal and abnormal postgadolinium enhancement of the nerve. Other pathologic processes can have a similar appearance, and MRI can assist in planning a targeted surgical biopsy. Additional adjunctive imaging studies such as positron emission tomography (PET) could help to narrow the differential diagnosis. However, the PET findings in this patient population have not been fully characterized.[8,11] We studied the combined use of MRI and PET for patients with a history of prostate cancer for a better understanding of the frequency of perineural spread and to generate an algorithm for diagnosis.

METHODS

The institutional review board approved the retrospective review of patients with a history of prostate cancer who had undergone both MRI and PET from 2005 to 2017. A choline PET scan database consisting of 10,815 scans from 3733 patients with prostate cancer was used to identify those cases with potential perineural spread. The database was searched for any patients with a history of prostate cancer and any of the following terms included in the report: perineural, lumbosacral plexus, sciatic, femoral, L4, L5, S1, S2, nerve, root, perirectal fascia, intradural, and cauda equina. The medical records were reviewed to collect demographic data (e.g., age and gender), document clinical history (e.g., oncologic timing, nerve-related symptoms, treatments), and PSA laboratory values. The PET and MRI scans from the identified patients were blindly reviewed for peripheral nerve involvement by 2 nuclear medicine (A.T.P. and M.A.N.) and 2 musculoskeletal (S.M.B. and B.M.H.) radiologists. The clinical history and imaging findings were compared using Student's t test and χ^2 analysis. Several cases from previous reported case reports or series were included in the present study.[3,5,10-13]

Pelvic MRI was performed using either 1.5 or 3T, with or without an endorectal coil. Perineural spread was evaluated using T1-weighted, T2-weighted, and postgadolinium-enhanced, fat-suppressed spoiled gradient echo recalled sequences. Positive findings of perineural spread included enlargement of the spinal nerves, lumbosacral plexus, or peripheral nerves (e.g., sciatic nerve) on T1-weighted sequences, hyperintense neural elements on T2-weighted sequences, and/or abnormal nerve enhancement after gadolinium administration. Choline and fluoro-2-D-deoxyglucose (FDG) PET used intravenous administration of ~10–20 mCi of C-11 choline and 10–15 mCi of F-18 FDG, respectively. Scanning was performed from the orbits through the thighs, beginning ~5 minutes and ~60 minutes after radiotracer injection for C-11 choline and F-18 FDG, respectively. Computed tomography (CT) or MRI fusion was used for attenuation correction and anatomic coregistration. Increased radiotracer uptake greater than the background level in a location thought to contain nerve was considered positive for perineural spread on PET imaging.

RESULTS

A total of 22 patients with a history of prostate cancer, previous pelvic MRI, and a PET scan report that listed terms indicative of perineural spread were identified. The average age of this male-only cohort was 73.0 years (range, 60–98). Most patients had previously been treated with combination therapy (68%) consisting of surgery plus hormonal therapy ($n = 1$) or radiotherapy ($n = 4$), or both ($n = 10$). The patients had a preponderance of documented extremity symptoms (64%), which included pain only ($n = 3$), pain and numbness ($n = 2$), or pain, numbness, and weakness ($n = 9$). The average duration from prostate cancer diagnosis to a positive imaging report of perineural spread was 10.5 years (range, 2–18). The median PSA level at the time of imaging was 2.15 ng/dL (range, 0.1–189).

After the consensus review of the MRI and PET imaging studies by the 2 nuclear medicine and 2 musculoskeletal radiologists, 16 of the 22 patients had evidence of perineural spread found on C-11 choline and/or F-18 FDG-PET (**Figure 1**). The 6 cases that were not thought to be true perineural spread either exhibited too low a degree of uptake as measured using the standardized uptake value or had findings thought to represent hypermetabolic pelvic lymph nodes. Five patients underwent both FDG and C-11 choline PET scans, with 100% concordance found between these studies. Of the 22 patients, 15 had perineural spread found on MRI. The lesions involved S1–S4 roots, sciatic nerve, and lumbosacral plexus. MRI also identified denervation involving the gluteus, piriformis, quadratus femoris, obturator internus, and hamstring muscles in 10 of the patients.

Twelve patients had positive findings found on both PET and MRI (**Figure 2**). No significant differences in these 12 patients were found in age, PSA value, previous radiation therapy use, or interval to diagnosis between those with and without positive MRI and PET findings (**Table 1**). Only 5 of these 12 patients had a PSA value of >4.0 ng/dL. A greater proportion of patients with positive MRI and PET findings had documented evidence of extremity pain, numbness, and/or weakness (83% vs. 40%; $P = 0.048$).

The present retrospective cohort of the 22 patients included 8 who had undergone underwent open fascicular nerve biopsy to determine whether the findings represented perineural spread of prostate cancer.[14] Of the 8 biopsy specimens, 4 were positive for prostate adenocarcinoma, 3 for inflammatory demyelinating disease, and 1 for MPNST. All 4 specimens with positive prostate perineural spread showed positive findings on both PET and MRI. The 1 patient with MPNST also had positive findings found on both PET and MRI. All 3 inflammatory lesions showed negative PET and variable MRI findings (**Figure 3**). Of the 14 patients without biopsy, 7 had positive MRI and PET findings, 4 patients had positive PET and negative MRI findings, and 3 patients had negative PET and positive MRI findings.

DISCUSSION

The objective of the present study was to uncover occult cases of perineural spread in patients with a history of prostate cancer. In addition, we sought to use pathologically confirmed cases to develop an algorithm for the care of patients with new nerve lesions and a history of pelvic malignancy. Using a PET scan

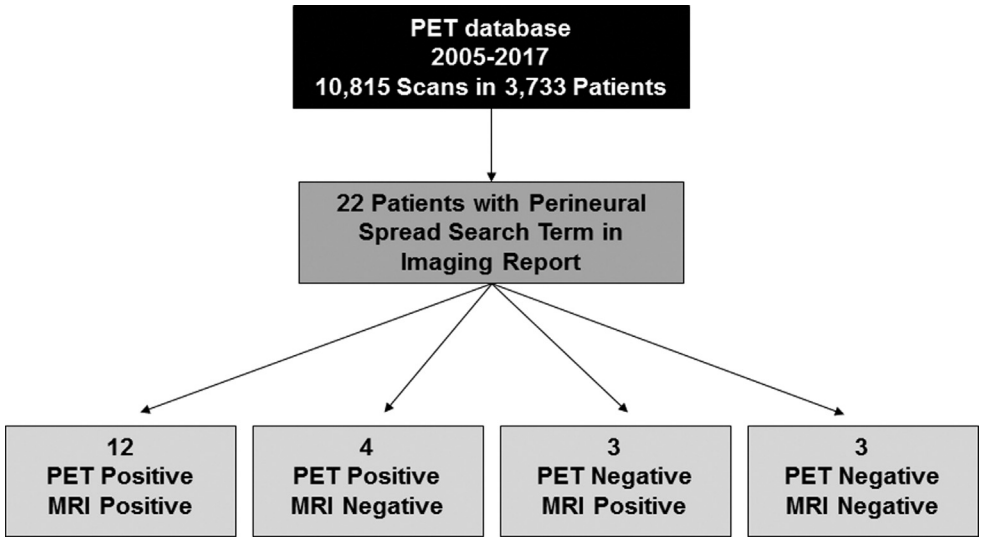

Figure 1. A choline positron emission tomography (PET) scan database was searched from 2005 to 2017 for patients with terms related to perineural spread. Twenty-two patients were identified with various degrees of positive and negative peripheral nerve PET and magnetic resonance imaging (MRI) findings.

database, 14 additional possible cases of perineural spread were identified and were combined with 8 previously biopsied cases (for a total database of 22 patients). All 5 patients with malignant histological findings (4 with prostate cancer and 1 with MPNST) had positive findings on both PET and MRI. In contrast, all 3 patients with benign inflammatory pathologic findings had negative PET findings.

Using the results from patients who had undergone biopsy, we believe that positive findings on both PET and MRI should be considered malignancy within the neural tissue (Figure 4). Of the 14 patients in our data set who had not undergone biopsy, 7 had positive MRI and PET scan findings. We suggest that these patients might have undiagnosed perineural spread and should be closely followed up for worsening neurologic function. The patient with a diagnosis of MPNST further emphasizes the need for biopsy, because patients who have received previous pelvic radiation might be at an increased risk of malignant nerve tumors.[9] Of our 22 patients, 4 had positive PET imaging findings but MRI findings negative for nerve abnormality. We hypothesized that this group might have malignancy in the tissue adjacent to the nerves (i.e., lymph nodes) and that the spatial resolution provided by MRI is able to rule out nerve involvement. A percutaneous needle biopsy might be indicated in this group to evaluate for cancer progression and to determine the need for additional cancer treatment as directed by their oncologist. Three patients had MRI-positive lesions but negative PET findings. This group likely does not have cancer progression. The findings more likely indicate radiation changes or neuroinflammation. A trial of steroids could be considered for this group if they are experiencing lower extremity neurologic symptoms. Finally, the group with negative findings on both MRI and PET likely represents a possible incorrect interpretation of the initial imaging findings. As the radiologic appearance of perineural spread becomes more well-known, we expect that the rate of false-positive and false-negative interpretations will decrease.

The purpose of distinguishing perineural spread from other non-neoplastic lesions is the divergent treatment recommendations, including steroids for inflammatory conditions or additional cancer treatment for perineural spread, such as radiation, chemotherapy, or hormonal therapy. However, neither the PSA value nor the clinical history can significantly contribute to the diagnosis of perineural spread.[3,5,9] Of the 22 patients, 64% had a PSA value <4.0 ng/dL and only 50% of the patients with histologically proven perineural spread of prostate cancer had abnormal PSA levels. The patient ultimately with a diagnosis of MPNST had a PSA value of 8 ng/dL. Despite systemic progression of the metastatic adenocarcinoma, we could not assume that the lesion in the nerve was prostate cancer. The PSA level becomes less reliable late in the disease course of prostate cancer (especially after surgery and hormonal therapy). Also, patients with perineural spread tend to present after many years, making this biomarker even less useful for the diagnosis of perineural spread. Although a larger percentage of patients with lower extremity symptoms were in the positive PET and MRI group, this clinical finding, in isolation, was nonspecific. All 3 patients with histologically confirmed inflammatory nerve lesions presented with pain, numbness, and weakness in the affected nerve distribution. Also, all 5 patients with histologically confirmed perineural neoplastic disease experienced lower extremity symptoms. Our data have demonstrated that the PSA level and symptoms should not be used to predict the presence of perineural spread. This further reinforces the need for a multimodal imaging algorithm to guide treatment.

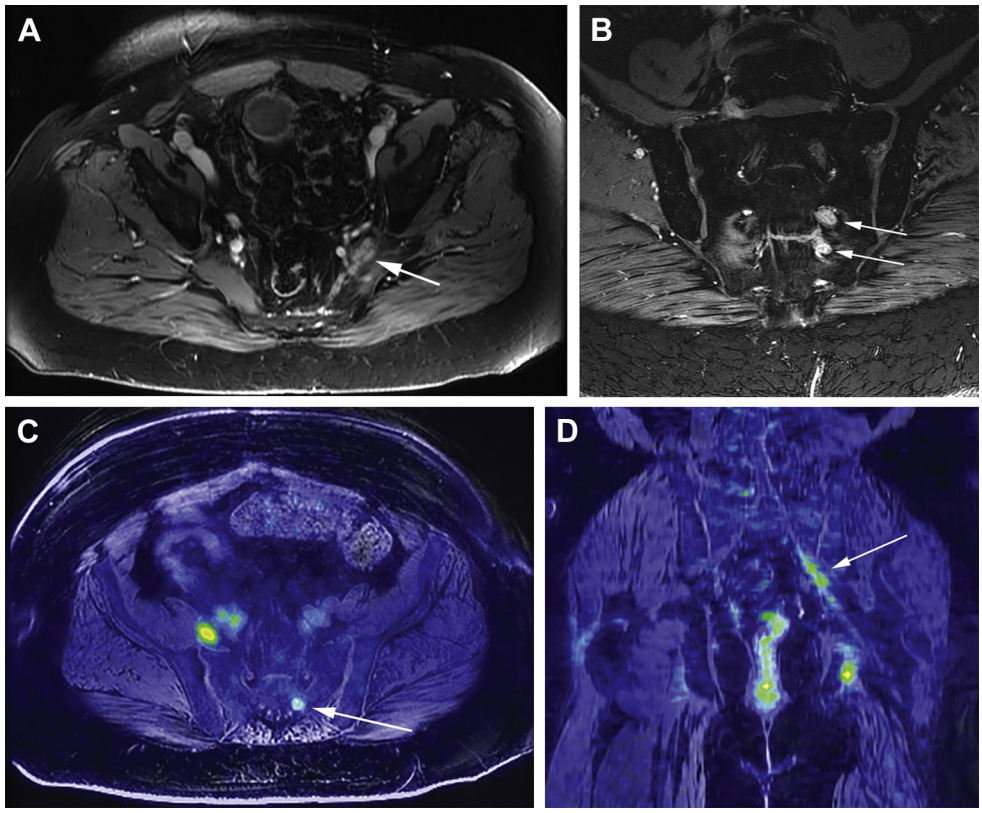

Figure 2. Imaging studies of a 65-year-old man with biopsy-proven perineural spread of prostate cancer. He presented with pain, weakness, and numbness 6 years after the original cancer diagnosis. (**A**) T1-weighted fat-saturated gadolinium-enhanced axial magnetic resonance imaging (MRI) scan demonstrating enlargement and enhancement of the left sciatic nerve (*arrow*). (**B**) T1-weighted fat-saturated gadolinium-enhanced coronal MRI scan showing enlargement and enhancement of the left S2 and S3 nerves (*arrows*). (**C**) Fused fluoro-2-D-deoxyglucose (FDG)-positron emission tomography/T1-weighted axial MRI scan demonstrating increased FDG uptake in the left S3 nerve (*arrow*). (**D**) Fused FDG-PET/T1-weighted fat-saturated coronal MRI scan showing increased FDG uptake along the left sacral nerves (*arrow*).

Table 1. Clinical Data

Variable	Negative PET and/or Negative MRI Findings	Positive PET and MRI Findings	*P* Value
Patients (*n*)	10	12	NA
Mean age (years)	70.3	75.3	0.195
Previous treatment included radiation	8 (80)	9 (75)	0.594
Time to diagnosis (years)	10.1	10.8	0.741
Abnormal PSA value (>4.0 ng/dL)	3 (30)	5 (42)	0.454
Presence of extremity symptoms	4 (40)	10 (83)	0.048

Data presented as *n* (%).
PET, positron emission tomography; MRI, magnetic resonance imaging; NA, not applicable; PSA, prostate-specific antigen.

Many different PET imaging tracers have been investigated for use in prostate cancer staging and restaging. European guidelines have recommended the use of 18-F sodium fluoride PET/CT for initial staging (only detects bone metastasis) and choline PET/CT (for PSA levels >1 ng/dL) or gallium-68 prostate-specific membrane antigen PET/CT (for low PSA levels) for recurrent disease.[15] Prostate cancer is known to have fewer GLUT transport proteins and, therefore, lower glucose uptake relative to other malignant tumors, limiting the sensitivity of FDG-PET.[16,17] Therefore, we suggest using choline PET or other prostate-specific PET radiotracers, when possible, to detect nerve invasion by prostate cancer. Despite this, we found 100% concordance between the FDG-PET and choline-PET scans in the 5 patients with biopsy-proven neoplastic perineural disease, highlighting the need to be cognizant of the potential for perineural metastasis regardless of the radiotracer used. These results can be extrapolated to other pelvic malignancies with new onset lumbosacral plexopathy, because perineural spread can also occur in bladder, uterine, and rectal

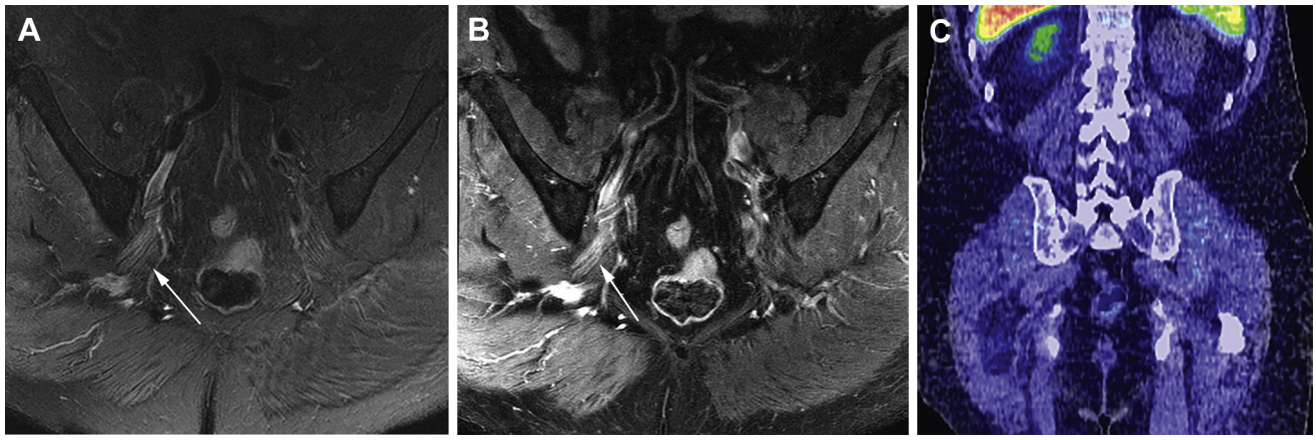

Figure 3. Imaging studies of a 79-year-old man with a history of prostate cancer after prostatectomy, hormonal therapy, and radiation presenting with right lumbosacral plexopathy 12 years after the initial diagnosis. Targeted nerve biopsy revealed an inflammatory demyelinating neuropathy without perineural spread. (**A**) T2-weighted coronal magnetic resonance imaging (MRI) scan demonstrating a mildly increased T2 signal and thickening of the lumbosacral plexus and L5 nerve (*arrow*). (**B**) T1-weighted, fat-saturated, gadolinium-enhanced coronal MRI scan demonstrating associated enhancement of the lumbosacral plexus and L5 nerve (*arrow*). (**C**) Fused C-11 choline positron emission tomography/computed tomography scan demonstrating no associated increased C11-choline uptake.

cancer,[10,18] posing diagnostic challenges similar to those with prostate cancer.

If available, integrated PET/MRI offers advantages for patients with a suspicion of harboring perineural spread. MRI provides high soft-tissue contrast and spatial resolution and the use of multiparametric sequences (e.g., gadolinium enhancement, diffusion-weighted imaging, and MRI spectroscopy) and is the best initial imaging modality for evaluating lumbosacral plexopathies.[8,19,20] This single integrated examination (instead of separate MRI and PET/CT examinations) is more efficient for the

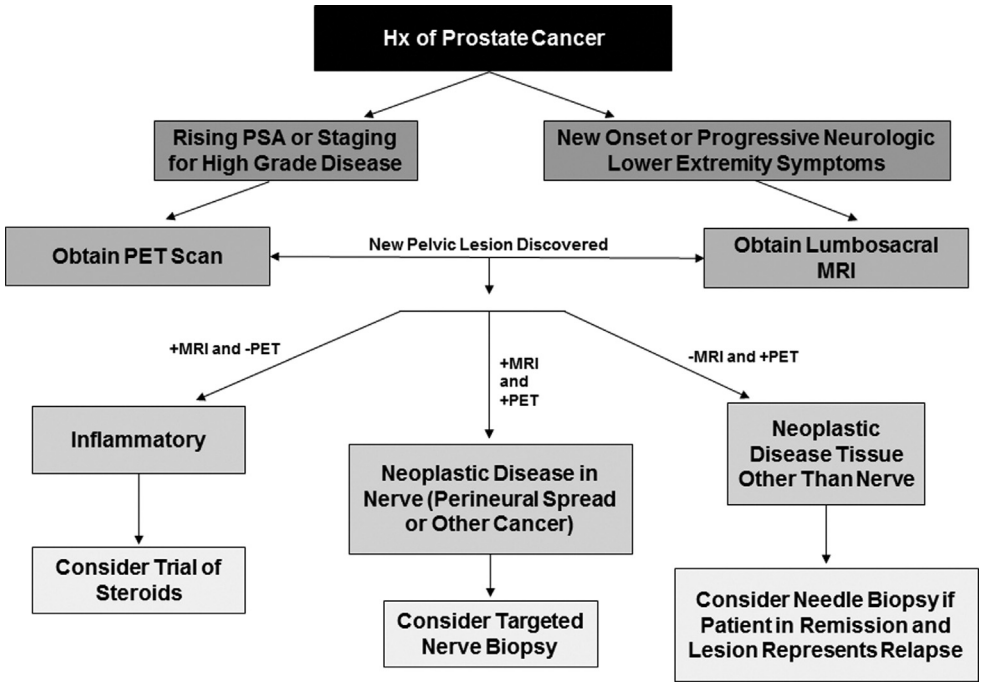

Figure 4. Algorithm for determining the possible need for biopsy in patients with a history of prostate carcinoma and peripheral nerve findings on magnetic resonance imaging and positron emission tomography scans.

patient, improves coregistration, and prevents unnecessary radiation.[19,21]

Using a PET imaging database, additional patients were identified who were suspected of having perineural spread. Although the true incidence of peripheral nerve involvement in patients with prostate cancer is unknown, these data indicate that it might be more common than initially thought. Although we have proposed this multimodal imaging algorithm to diagnosis perineural spread, we acknowledge that most patients in our study had not undergone biopsy. Therefore, we cannot know for certain how many of these patients had true nerve involvement. We, therefore, could not calculate the sensitivity and specificity for the ability of multimodal imaging to diagnose perineural spread. Furthermore, our study identified patients using positive radiology reports and because this entity is underrecognized, we undoubtedly underestimated its incidence. Underreporting of neurologic signs and symptoms could have also occurred owing to insufficient neurologic history and physical documentation by the unsuspecting treating urologic surgeon. Because MRI is becoming more common for patients with prostate cancer, a thorough study specifically evaluating the presence of perineural spread on routine MRI is needed.

CONCLUSIONS

The true incidence of perineural spread in patients with prostate carcinoma is unknown. Patients found to have neoplastic disease on nerve biopsy had positive findings on both pelvic MRI and PET scans. Using a PET scan database and this multimodal imaging approach, several potential cases of perineural spread were uncovered. Perineural spread is likely more common than previously believed, and further analysis of routine MRI scans is needed to understand its frequency. Using positive findings on multimodal imaging with PET and MRI should be the standard of care in the evaluation of patients with prostate cancer suspected to have perineural spread.

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