Detection and Management of Isolated Lymph Node Recurrence in Patients with PSA Relapse

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Biochemical recurrence of prostate cancer after radical surgery or external-beam radiation therapy (prostate-specific antigen [PSA] relapse) remains a major concern for the management of patients with prostate cancer and occurs in approximately one third of men so treated. Without salvage therapy, 65\% develop clinically apparent skeletal metastases within 10 yr\textsuperscript{[1]}. The appropriate diagnostic and therapeutic management of these patients continues to evolve, but it is essentially based on distinguishing between local recurrence (which may be amenable to salvage irradiation or salvage prostatectomy) and distant disease (which traditionally requires systemic treatment with either antiandrogen hormonal therapy or chemotherapy). Endorectal magnetic resonance imaging (MRI) has evolved as the most reliable structural imaging test for detecting local recurrence. Historically, computed tomography (CT), bone scan, or antibody imaging were used in the assessment for distant disease, but none of these tests identifies systemic disease at an early state. Therefore, many investigators have turned their interest to positron emission tomography (PET), more recently PET in combination with CT in a single machine (PET/CT). Combined PET/CT shortens the examination time by about 50\%, and the CT images provide necessary anatomic information to localize the area of abnormal radiotracer uptake. Among various radiotracers for PET imaging of prostate cancer, labeled acetate and choline appear most promising and may (realistically) identify local recurrence or distant disease in 50–70\% of patients with PSA relapse\textsuperscript{[2–4]}. However, the total number of patients studied with these agents is still relatively small, and the results are variable. Some investigators claim sensitivities of nearly 100\%, which is difficult to believe, whereas others emphasize limitations in patients with lower PSA values\textsuperscript{[4]}.

The study by Scattoni et al in the current issue of European Urology\textsuperscript{[5]} highlights some of the limitations of PET in detecting small lymph node metastases in patients with prostate cancer. Twenty-five patients with PSA relapse (PSA mean: 4.0 \pm 5.4 ng/ml; range: 0.23–23.12) and no evidence for local recurrence in the prostate bed or osseous metastases were imaged with \textsuperscript{11}C-choline PET/CT to identify isolated lymph node metastases. All 25 patients then underwent an extended pelvic lymph node dissection in the obturator fossa and along the bilateral external and internal iliac vessels. Thirteen patients also underwent retroperitoneal lymph node dissection, which included the common iliac nodes and extended proximally up to the level of the renal vessels, either based on abnormal PET/CT findings or because of clinical suspicion. Visually apparent lymph nodes were removed, whereas blinded biopsies were taken from areas where no lymph nodes could be identified by the surgeon. The mean number of nodes removed was 22 \pm 17 (range: 4–31). \textsuperscript{11}C-choline
PET/CT showed abnormal uptake in lymph nodes in 21 patients (13 in the pelvis and 8 in the retroperitoneum), of which 19 were confirmed by histopathology (i.e., 19 true positive and 2 false positive). By comparison, CT or MRI revealed abnormal lymph nodes in 12 patients; in 8 cases, these abnormalities were also apparent on PET/CT, whereas the other 4 findings were false positive. In other words, independent structural imaging did not provide any additional information. When analyzed by nodal sites (a total of 63 sites), the PET/CT was true positive in 20, false positive in 3, true negative in 29, and false negative in 11 sites, providing a sensitivity and specificity of 64% and 90%, respectively. There was no apparent difference in sensitivity between individuals with PSA > 2 ng/ml as compared to those with PSA > 2 ng/ml. However, small metastatic nodes are more likely to be missed (the mean diameter of true-positive nodes was 15 mm as compared to 6 mm in false-negative nodes). Thus, although PET/CT proved helpful in localizing lymph node metastases in patients with PSA relapse, the sensitivity of 64% remains far from desirable. Technical details of CT/MRI (slice thickness, sequences, use of contrast) are not provided. Further, 11C-choline may be a suboptimal clinical radiotracer because of the need for a nearby cyclotron (20 min half-life time for 11C) and the often noisy image quality.

How could this data by Scattoni et al [5] be applicable in clinical practice? The answer to this question may be found in the current debate regarding the extent of lymph node dissection during radical prostatectomy. There is growing concern that limited or even “standard” pelvic lymph node dissections grossly underestimate the extent of occult metastatic disease in patients with prostate cancer [6–8]. In many contemporary series, they yield of positive nodes is in the range of 3–10% when patients undergo a pelvic lymph node dissection that assesses the obturator and hypogastric regions [9]. In contrast, when the area of lymph node dissection is extended to include all primary lymphatic drainage regions, the yield of positive nodes is as high as 20–25% [6,7,10]. Of note, in one of these studies [10], 63% of men harbored metastatic lymph nodes outside the regions that many consider part of a standard lymphadenectomy for prostate cancer, and the percentage of positive nodes was higher than predicted by nomograms. There may be at least three reasons for the higher yield of positive nodes with extended dissections: a larger fraction of patients with advanced disease (PSA > 10 ng/ml and Gleason score ≥ 7) [10], which are known predictors for lymph node involvement; the histopathologic technique used for lymph node assessment (higher yield with immunohistochemistry than with standard hematoxylin and eosin staining); and finally the surgical technique, that is, extending the field of lymph node dissection to include all primary lymph node drainage regions and thus harvesting a larger number of nodes for histopathologic analysis.

Extended lymph node dissection during prostatectomy is certainly a staging procedure, but it is less clear whether and to what extent the surgical removal of metastatic nodes also translates into a measurable decrease in the rate of biochemical recurrence and subsequent clinical metastatic disease [9]. Similar to the primary setting, the surgical removal of isolated nodal recurrence in patients with PSA relapse might be curative or delay the progression of disease, but this also remains unproven. The assumption for such a treatment is that metastatic disease in pelvic lymph nodes was already present at the time of initial treatment but was not properly addressed by the surgical or radiation therapy received. It is further assumed that these lymph nodes potentially represent the sole site of disease, so that their removal may provide a measurable improvement in patient outcome. In any event, lymph node dissection in patients with PSA relapse should only be done after local recurrence and distant disease at other sites are excluded with reasonable certainty, perhaps with a combination of endorectal MRI and PET/CT with choline or acetate. To minimize the invasiveness, one might also consider a laparoscopic removal of isolated lymph node disease. However, this would require an imaging test that could accurately determine the complete extent and specific location of metastatic nodal disease. As the study by Scattoni et al [5] shows, neither structural imaging nor PET/CT is currently sufficiently sensitive for this purpose. Instead, a positive PET/CT study may perhaps provide guidance to the urologist when lymph node dissection in patients with PSA relapse.

In conclusion, Scattoni et al have provided promising data, but much work remains to be done to determine the true clinical utility of PET/CT for detecting isolated lymph node recurrence in patients with early PSA relapse.

References


