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Sensitivity of Frozen Section Examination of Pelvic Lymph Nodes for Metastatic Prostate Carcinoma

I read with particular interest the article by Davis1 about the sensitivity of frozen-section examination of pelvic lymph nodes for metastatic carcinoma. The section in which the results of frozen section are compared with imaging techniques found in the Medical Literature Analysis and Retrieval System (MEDLARS) literature research deserves comment.

The author’s conclusion that “... frozen section diagnosis of pelvic lymph nodes ... is more sensitive for the diagnosis of prostate carcinoma in pelvic lymph nodes than is MRI because more than half of the metastases are smaller than the 1-cm resolution limit of the MRI,” may be misleading and is not correct.

The upper limit of the spatial resolution of magnetic resonance imaging (MRI) and computed tomography (CT) is much smaller than 1 cm. It depends on many factors, such as field of view, matrix size, slice thickness, image quality (signal-to-noise ratio, motion artifacts) and contrast between the object and surrounding structures. Using a three-dimensional imaging technique, we achieved an in-plane resolution of 1.3 mm × 1 mm and were able to visualize lymph nodes with a diameter of 4 mm.2

Also, the literature search on imaging techniques is incomplete. The reviewed number of articles on CT and MRI is far too low; for example, the review does not include the article by Rifkin et al.,3 which includes more patients (185) investigated with MRI than the compiled data of the articles cited by the author. In this series, the sensitivity was only 4%.

In general, it is believed that MRI is equal to CT for lymph node imaging. The advantage of CT over MRI is that fine-needle aspiration of a lymph node mass may be more easy to perform. In contrast to lymphangiography, in which metastases are visible as filling defects of 4 mm or more in diameter,3 MRI and CT do not allow direct visualization of lymph node metastases. The main criteria to assess the presence of lymph node metastases is the axial diameter of the lymph node. Perhaps the author confused “resolution limit” with what is considered as the upper limit of a normal sized lymph node. However, criteria for positive lymph nodes are arbitrary. In the cited articles, the upper limit of normal varies from 1 cm6 to 1.5 cm.7 There is a general tendency to lower the upper limit of normal. Recently, Vinnicombe et al.,9 who found that only 2% of normal lymph nodes have a maximum short axis diameter of larger than 1 cm, suggested that the sensitivity of CT in depicting lymph nodes may be improved by adopting lower limits of normal. These may become 7 mm for internal iliac, 8 mm for obturator, 9 mm for common iliac, and 10 mm for external iliac lymph nodes. Using a three-dimensional imaging technique, we could add the shape of the lymph node in the judgment; round nodes with a diameter of 8 mm and an index of 0.8 (shortest axial diameter divided by the long axis) or less were considered abnormal. With these criteria, the figures for sensitivity, specificity, and accuracy were 58%, 96%, and 92% in 62 patients (data presented at the 81st Annual Meeting of the Radiologic Society of North America, Nov–Dec, 1995). Van Poppel et al.10 consider even lymph nodes of 6 mm in diameter on CT to be positive. Calculated figures for sensitivity, specificity, and accuracy were 77.8%, 96.6%, and 93.7%, respectively. When fine-needle aspiration biopsy was performed to evaluate suspected nodes, the calculated figures were 77.8%, 100%, and 96.5%, respectively. These figures are unique and may be not representative for imaging in general.

However, the argument that frozen section is more sensitive than CT or MRI does not implicate that there is no place for imaging as is suggested in the article by Davis.1 Lymph node metastases detected by imaging will considerably save financial costs, morbidity, hospital stay, and patient discomfort. However, only 10% of patients who are candidates for surgical cure have metastatic lymph node disease.11,12 Therefore, cross-sectional imaging is not indicated for all patients. It should be restricted for patients who are at high risk for having lymph node metastases depending on prostate specific antigen, stage, and the Gleason biopsy score. Wolf et al.13 have estimated that when the sensitivity of imaging was 36% (baseline derived from literature), imaging would be beneficial when the probability of metastases was 32% and
when suspected lymph nodes were confirmed by fine-needle aspiration biopsy.

In conclusion, imaging is still of value in a selected group of patients who are at high risk for lymph node metastases to prevent them from an unnecessary operation. In my opinion, in this group of patients, the upper limit of normal should be less than 1 cm.

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Author Reply

I thank Dr. Jager for his comments. He is correct regarding my confusion between the spatial resolution limit of the imaging technique and the criteria for metastasis (the axial diameter of the lymph node). The purpose of my study was to assess the diagnostic efficiency of frozen section and then compare the results with the only other modality available for the direct assessment of lymph node metastases prior to prostatectomy—imaging.

I did miss the 1990 article by Rifkin et al.,1 which indicates that magnetic resonance imaging and computed tomography had high specificity (96%) but very low sensitivity (4%) for the diagnosis of lymph node metastases “because neither technique has the ability to identify microscopic spread of disease.”1 In 1995, using either a 4-mm resolution limit for lymphangiography or a 6-mm limit for computed tomography, the best imaging techniques cited by Dr. Jager, 18 of 39 or 22 of 39 patients in my series2 still would not have been detected due to the microscopic size of their metastases below these respective resolution limits. Accepting Dr. Jager’s criticism, I would change the conclusion of the paper to “Frozen section analysis is more sensitive for the diagnosis of prostate carcinoma in pelvic lymph nodes than are imaging techniques because 46% of the metastases in our series are smaller than the lowest (4 mm) resolution limit of the imaging techniques to be reported by Barentsz et al.”2

Imaging is of value in identifying patients who are at high risk for lymph node metastases to prevent them from an unnecessary operation.3 Regardless of imaging technique or user, with an upper limit of normal lower than 1 cm, half of our patients with metastases would still be missed and we are therefore unable to identify them in advance of lymphadenectomy.

The rapid changes taking place in both the diagnosis and treatment of prostate cancer are reflected in editorials and articles concerned with prostate specific antigen (PSA), biopsy grade, and treatment variables in the literature5–8 concurrent with the submission and publication of my paper. Imagery face the same dilemma as surgeons; how to select patients who will benefit by use of a procedure. Strategies for detecting lymph node metastases,7,8 including imaging with or without fine-needle aspiration of “positive” lymph nodes and two-stage (open or laparoscopic) lymphadenectomy, attempt to preselect patients at risk for lymph node metastases by means of PSA, biopsy grade, and clinical staging.

Can current clinical or laboratory parameters preselect patients who are at risk for lymph node metastases? Using PSA levels and biopsy grade, we have been unable, retro-
spective, to differentiate false-negative frozen-section patients (microscopic lymph node disease) from true positive patients (unpublished data). Only at the extremes of PSA and grade can we predict lymph node metastases with greater efficiency than by frozen section and, for the majority of our patients, there is no relationship between PSA and biopsy grade, and size of the metastasis. Metastasis does not necessarily result in lymph node enlargement.

As prostate cancer is diagnosed “earlier,” I anticipate that a greater proportion of metastases will be occult,10 for the diagnosis of which current routine clinical laboratory tests and imaging are inadequate. The application of new diagnostic technology (such as polymerase chain reaction amplification10 for the detection of currently occult cancer cells in the blood stream or tissues obtained with minimally or noninvasive techniques with imaging localization) is needed for the accurate and cost-effective staging and treatment of prostate cancer.

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Cost Effectiveness and Outcome Assessment of Magnetic Resonance Imaging in Diagnosing Cord Compression

I read with interest the recent article of Jordan et al., ([“Cost Effectiveness and Outcome Assessment of Magnetic Resonance Imaging in Diagnosing Cord Compression”]) regarding cost-effectiveness of magnetic resonance imaging (MRI) versus myelography for diagnosing malignant epidural spinal cord compression. I would like to raise some issues that might influence their model.

First, the authors do not address the issue of how much of the spinal column was imaged in the MRI versus the myelography group. When myelography is utilized to diagnose cord compression, the standard of care has been a complete myelogram.1 If high-grade block is present, this may require a second injection of dye above the level of the block. In contrast, the mean cost of $2283 for MRI patients in Jordan’s study suggests that, on average, fewer than two of three spinal segments (cervical, thoracic, and lumbosacral) were imaged. Therefore, patients receiving myelograms were more likely to have complete spinal imaging. Although more expensive, myelography might actually result in a better neurologic outcome, since 10% to 30% of patients with epidural disease at one spinal site will have epidural disease at a remote site, as suggested by subtotal spine MRI.2,3,4 Costs in Jordan’s two groups might have been quite similar had each group had the entire neuraxis imaged. From the neuro-oncologic viewpoint, imaging the entire spine is preferable to imaging only the segment clinically suspected of harboring epidural tumor.

Second, the authors state that the cost of a false positive neuroimaging study includes the cost of radiation followed by the cost of surgery, implying that standard treatment consists of this combination. They admit that, “radiation will not be followed by surgery in all cases.” In fact, treatment for spinal cord compression generally consists of radiation therapy alone. Surgery is sometimes employed as initial therapy in patients requiring a tissue diagnosis, patients with radioresistant tumors, and patients with spinal instability. Radiation followed by surgery is not standard treatment for spinal cord compression, although this sequence of events may occur in patients who deteriorate during radiation, or in patients who eventually relapse following an initial response to radiation.

Finally, although spinal cord compression is indeed a neurologic emergency, and although pretreatment neurologic status is the most important predictor of treatment outcome,5,6,7,6,8 I am aware of no data which supports the authors’ hypothesis that a 16-hour average delay.