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REVIEW

MR imaging of pelvic lymph nodes

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Abstract

The occurrence of metastases to pelvic lymph nodes profoundly affects the prognosis of pelvic malignancies, making accurate staging crucial for selecting appropriate treatment. Modalities for the detection of metastatic lymph nodes are lymph node dissection, lymphangiography, and non-invasive techniques such as computed tomography (CT) and magnetic resonance imaging (MRI); the role of these techniques will be reviewed. Although this review will focus on prostate cancer, the statements may be generalised for other malignancies, as the metastases in pelvic lymph nodes have a similar pattern for other tumors.

Introduction

The occurrence of metastases to pelvic lymph nodes profoundly affects the prognosis of pelvic malignancies, making accurate staging crucial for selecting appropriate treatment. Modalities for the detection of metastatic lymph nodes are lymph node dissection, lymphangiography, and non-invasive techniques such as computed tomography (CT) and magnetic resonance imaging (MRI); the role of these techniques will be reviewed. Although this review will focus on prostate cancer, the statements may be generalised for other malignancies, as the metastases in pelvic lymph nodes have a similar pattern for other tumors.

Pelvic lymph node dissection (PLND)

PLND has traditionally been an integral component of prostate (pelvic) cancer staging. Pathological examination of lymph node tissue remains the gold standard for determining whether or not lymph node metastases are present. However, there has been recent interest in identifying patients for whom lymph node dissection may not be justified on the basis of cost and potential morbidity[1].

PLND is an expensive, invasive procedure, with attendant complications, and appears to have no therapeutic value[2]. Reported complications of PLND are obturator nerve injury, trauma to major vessels, thromboembolic events, lymphocoele formation, chronic lower extremity and genital edema and infection[3].

The advent of prostate specific antigen (PSA) screening and increased clinical awareness have led to considerable stage migration and a low incidence of lymph node involvement in contemporary radical prostatectomy series[4]. Multiple models and nomograms combining PSA, clinical stage and Gleason score have been developed to predict the probability of metastatic disease[5–7]. Others have proposed PSA and Gleason score cut-off points for selecting patients in whom the risk of nodal disease is low, obviating the need for PLND. Essentially, these cut-offs would define an acceptable percentage of patients with potentially detectable metastatic disease who would nevertheless undergo radical prostatectomy. Currently, PLND is not carried out in patients deemed to be at low risk for lymph node metastasis. Using a false-positive rate of 3%, Bluestein *et al.* estimated that 25% of patients with clinically localised disease could be spared PLND[6]. Rees *et al.* constructed a predictive model to identify patients with less than 3% likelihood of harboring lymph node disease[8]. Campbell *et al.* observed similar results, in that 73% of their patients were at low risk and the rate of positive lymph nodes was only 2.2%[9]. How can an acceptable false-negative

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rate be defined if PLND is not carried out? When using any of these models and nomograms, a small percentage of patients harboring positive lymph nodes are in the low-risk group and subsequently undergo radical prostatectomy. It seems logical that the benefit of omitting PLND in 50–70% of patients would outweigh the 2–5% of patients with missed positive lymph nodes. Rees *et al.* stated that physicians evaluating patients with newly diagnosed prostate cancer should be willing to accept a false-negative rate of 1.8% or less when deciding whether to perform PLND for evaluation[8]. In general, it is advisable to omit PLND in patients with PSA <10 ng/ml and Gleason score <7[2,10–14], or PSA <20 ng/ml and Gleason score <7[10,15]. The threshold, however, has only been evaluated objectively by Meng and co-authors by using a formal decision analysis[16]. Even assuming that PLND and frozen section analysis of lymph nodes is 100% sensitive, their model supports performing PLND only in patients with a greater than 18% prevalence of positive lymph nodes. The sensitivity of PLND is limited by the fact that positive nodes will go unnoticed in 12% of positive-node patients and 5% of patients subjected to lymphadenectomy. This is caused by the fact that these patients have isolated metastases to the common and external iliac nodes, which are not included in the PLND generally used in prostate cancer[17,18]. These findings are supported by Barth *et al.*[19] and Weingartner[20]. They found that the detection of lymph node metastases, and consequently the prognostic accuracy, is mainly influenced by the total number of lymph nodes examined. At least 13–20 nodes should be removed. Furthermore, the efficacy of frozen section analysis of pelvic nodes has also been questioned[21]. Reported false-negative results are 100%[22], 40%[23], 33%[1,24–28], 30%[4,29], 23%[30], 19-7%[31].

Lymph node metastasis may be detected by methods other than open PLND. Minimally invasive techniques, such as laparoscopic and mini-laparotomy PLND, are well described and provide comparable information and improved patient recovery. Although the complication rate of laparoscopic dissection is lower, it requires general anaesthesia and hospitalisation. However, they offer no advantage with respect to surgery time and cost[9–12,32–36].

Staging lymph nodes: imaging

A non-invasive, reliable method for detecting and staging nodal metastasis would reduce unnecessary surgery. Currently, there are five imaging techniques described for nodal staging: lymphangiography, CT, MRI, prostascint radio-immunoscintigraphy, and ^{18}FDG–PET. Bipedal lymphangiography is no longer used as a screening method, although it has the capacity to show micro metastases in normal-sized nodes. Its inability to depict internal iliac nodes and its potential invasiveness are major drawbacks.

CT scanning and MRI

Cross-sectional imaging modalities like CT and MRI have a low sensitivity (36%)[22,29,30,37–62] because both modalities use the non-specific criterion of size to distinguish between normal and malignant nodes, and because both normal nodal and metastatic tissue have the same signal intensity. The most generally accepted criterion for a node to be metastatic on CT and MR imaging is size. A minimal axial diameter of 10 mm or less is considered to be normal.

Recently, three-dimensional high-resolution MRI techniques have been used, which has allowed not only determination of nodal size but also of nodal shape[3]. These authors considered round nodes with a minimal axial diameter of more than 8 mm to be metastatic, in addition to oval nodes with a size of more than 10 mm[49]. Using the additional feature of shape improved their sensitivity to 75%. However in the same study, metastases in normal-sized lymph nodes (25%) were still going unnoticed.

Although fast dynamic MRI has been shown to improve sensitivity by showing fast and high enhancement in metastatic nodes, specificity has decreased. In addition, fast dynamic is further limited by its low resolution and pronounced vascular artifacts[63].

Thus staging PLND remains the most sensitive method for assessing lymph node metastases and continues to be the first step in the management protocol. Cost-effective analysis performed by Wolf *et al.*[29] pointed out that imaging should be restricted to patients with a high probability of lymph node metastases. These authors stated that when the probability of positive nodes based on PSA level and clinical stage was 32%, the sensitivity of the imaging method must be 36% to be beneficial. When the sensitivity was 25%, as in their series, prior probability should be 45%. Thus they concluded that imaging was beneficial only when the pretest probability of lymph node metastasis was high. The most important parameter was the sensitivity of cross-sectional imaging for lymph adenopathy. Pelvic imaging combined with fine-needle aspiration has also been investigated. The data of Wolf *et al.* suggest that only a subset of patients at high risk for lymph node metastasis benefits from cross-sectional imaging and preoperative lymph node sampling.

Prostascint radio-immunoscintigraphy and ^{18}FDG–PET

Although very promising in metastatic lung cancer, the role of ^{18}FDG–PET scanning is limited in the urinary tract region, as ^{18}F-fluorodeoxyglucose accumulates as part of the physiologic process in this area. This makes an evaluation of metastases at this site difficult[64]. This method is further limited by its low uptake in metastatic nodes, especially in prostate cancer. In a study using PET

in 64 patients with urinary bladder cancer, Bachor *et al.* obtained a sensitivity of 67% and a negative predictive value of 84%. In addition, their reported specificity of 86% is lower than those obtained with CT and MRI[65]. Heicappell *et al.* obtained a sensitivity of 65% with their data[66].

With radio immunoscintigraphy (prostascint) in patients with prostate cancer, Hinkle *et al.* and Manyak *et al.* found a sensitivity of 75 and 62% respectively[52,67].

Although the results of prostascint radio immunoscintigraphy and ^{18}FDG–PET are slightly better than those of CT and MR imaging, they are not high enough to replace PLND. A negative prostascint scan may not eliminate the need for PLND, due to low sensitivity for small volume disease.

New developments: MRI after intravenous injection of a lymph node specific contrast agent

Previous reports have shown that the information about lymph nodes on MR images can be improved by pharmaceutical manipulation of tissue proton relaxation times. Ultra small super paramagnetic iron oxide particles (USPIO) with a long plasma circulation time have been shown to be suitable as an MR contrast agent for intravenous MR lymphangiography[68,69]. After intravenous injection, the USPIO particles are transported to the interstitial space and from there through the lymph vessels to the lymph nodes. Once within normally functioning nodes, the iron particles are taken up by macrophages; due to the T2*—and susceptibility effect of iron oxide, they reduce the signal intensity of normal lymph node tissue in which they accumulate, thus producing a negative enhancement. In areas of lymph nodes that are involved with malignant cells, macrophages are replaced by cancer cells, which lack reticuloendothelial activity and are unable to take up the USPIO particles. Other conditions in which the uptake may be decreased include inflammatory nodes, as was the case in two patients in our study. In addition, due to increased vascular permeability and increased diffusion in cancer tissue, there is leakage of USPIO particles into the metastatic areas, which produces a low local concentration and non-clustering of USPIO particles at these metastatic sites[70]. Through their T1 relaxivity, this can induce an increase in signal intensity on T1-weighted images, producing positive enhancement[71–73]. Thus the ability of post-contrast MRI to identify metastatic areas in the lymph nodes depends primarily on the degree of uptake of USPIO by the macrophages in normal lymph node tissue and the leakage of USPIO particles in the metastatic area itself. Twenty-four hours after intravenous injection of USPIO, normal lymph node and malignant tissue have different signal intensities on MR images, thus this non-invasive technique may result in the detection of metastatic deposits in normal-size nodes[71].

Thus far only two papers have appeared using this technique in the evaluation of pelvic malignancies, reporting a sensitivity of 82 and 86%[71,74]. Other papers include lymph node evaluation in other areas, predominantly head and neck and chest. Reported sensitivities (mean 91%, range 84–100%) are higher compared to pre-contrast MRI[75–79]. As these authors did not use high-resolution techniques, they had limited visualisation of small (<8 mm) lymph nodes.

A pilot study was performed at Mass General in Boston, Charite in Berlin and UMC in Nijmegen, on patients with histologically proven bladder and prostate cancer. High-resolution techniques (at 1.5 T using a body phased-array coil) on post-USPIO MRI significantly improved the rate of detection of small nodal metastases in normal-sized nodes (<8 mm). Normal nodal tissue showed signal loss 24–36 h post injection. Metastases showed equal or higher signal. The 3D T1-weighted sequence vessels, especially veins, showed high signal intensity, thus facilitating separation from nodes. On the T2*-GRE sequence in most patients the vessels showed low signal intensity. Sensitivity and accuracy and negative predictive value showed a significant improvement, using post USPIO, to 85, 87 and 92%. This was due to the detection of metastases in normal-size nodes. During the slow (30 min) infusion of the USPIO contrast, only two patients showed minor side effects (low back pain), caused by too rapid an infusion. After slowing down the infusion rate the symptoms decreased, and no further treatment was needed.

Conclusions

PLND is unnecessary in the subset of patients in whom the risk of lymph node involvement is less than 18%. CT and MRI do not have the desired sensitivity in identifying metastases to replace PLND. Only patients at very high risk (36%) for lymph node metastasis benefit from CT and MRI using preoperative fine-needle aspiration biopsy of enlarged nodes. Although new techniques like prostascint radio immunoscintigraphy and ^{18}FDG–PET have a higher sensitivity than CT and MRI, it is not high enough to replace PLND. Initial results with MR lymphography show a promising sensitivity (85%) and negative predictive value (92%) in the detection of nodal metastases of prostate and bladder cancer. If the results of a pilot study can be confirmed in a multicenter study, PLND may be avoided in most patients with prostate cancer.

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