Lymphtrophic Nanoparticles in Prostate Cancer

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Lymph Node Status in PCa: Why Worry

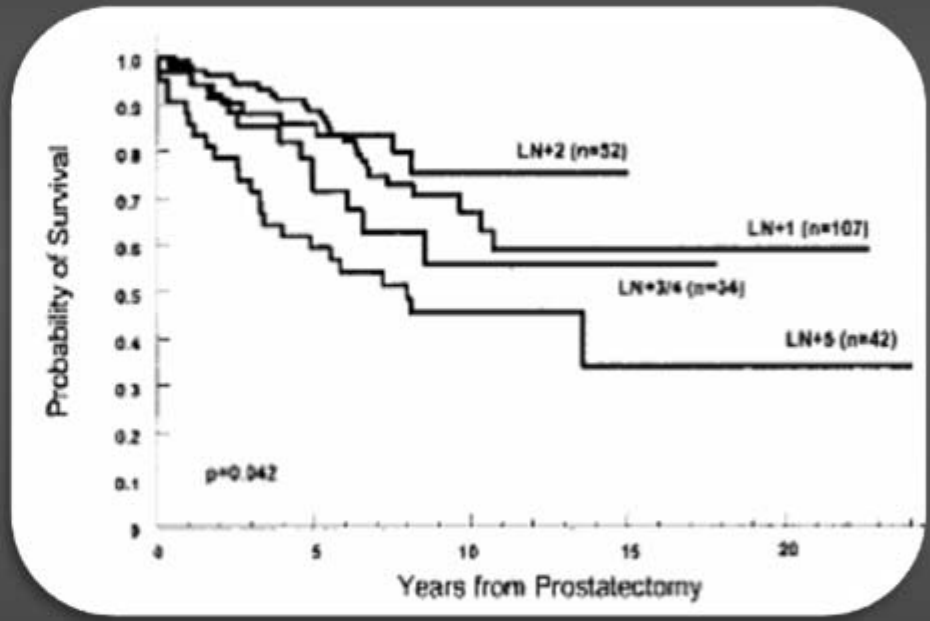
- Decisions on therapy
- Predicting recurrence and assessing prognosis

Therapy Decisions

- Deciding on appropriate therapy
  - Node positive
    - Non surgical therapy

Patient with Prostate Cancer

- Determine prognosis
  - Number of LN involvement affects disease progression and survival rate
    - 1-2 positive nodes (Recurrence free survival of 70 %)
    - > 5 positive nodes (Recurrence free survival 49 %)



Daneshmand et al
J Urol 2004; 172:2252

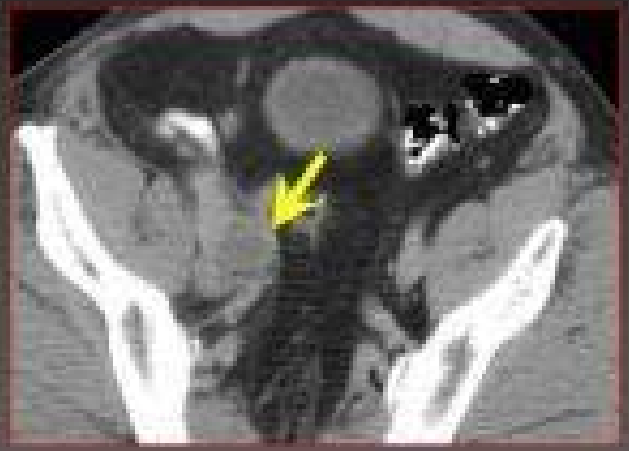
Lymph Node Metastases

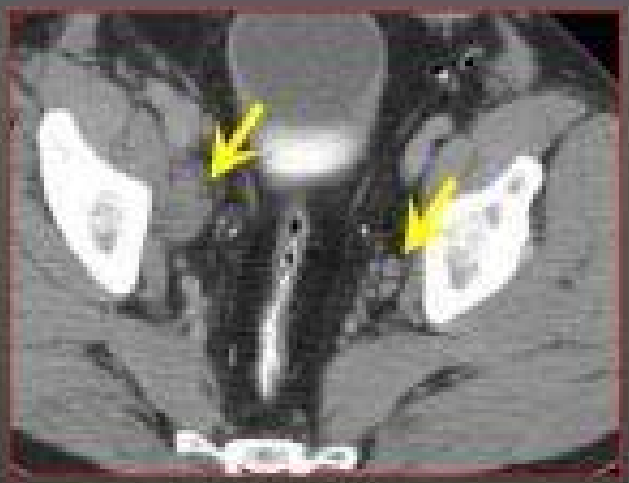
- Era of PSA screening
  - Incidence of pelvic nodal metastases dropped to < 10 % compared to 40-60% in past
- Caveats

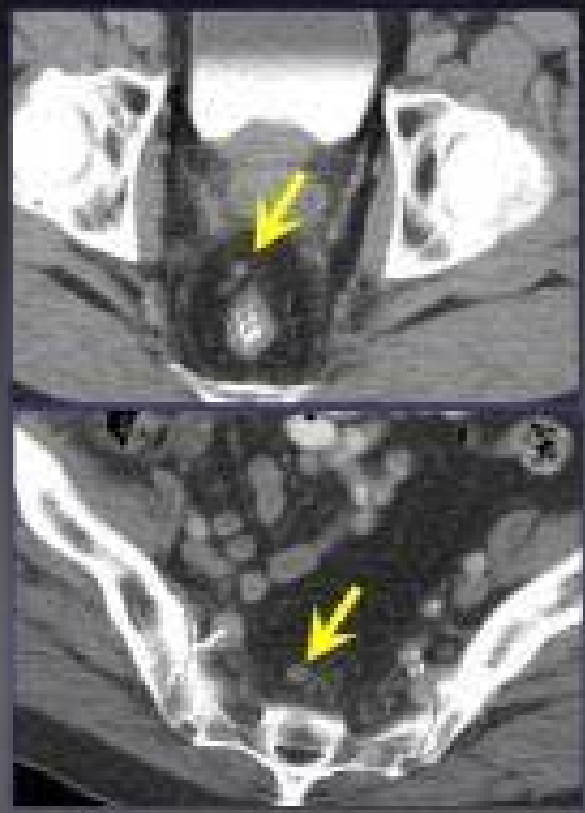
Lymph Node Metastases

- Caveats
  - Most studies excluded patients with high risk or aggressive prostate cancer
    - Neoadjuvant androgen ablation
    - Patients who has positive nodes with extended nodal dissection
- Although overall percentage of patients with positive LN has declined, there remains significant numbers of patient with LN positive cancer (39 % in high risk patients)

Swanson et al; Cancer 2006; 107; 439







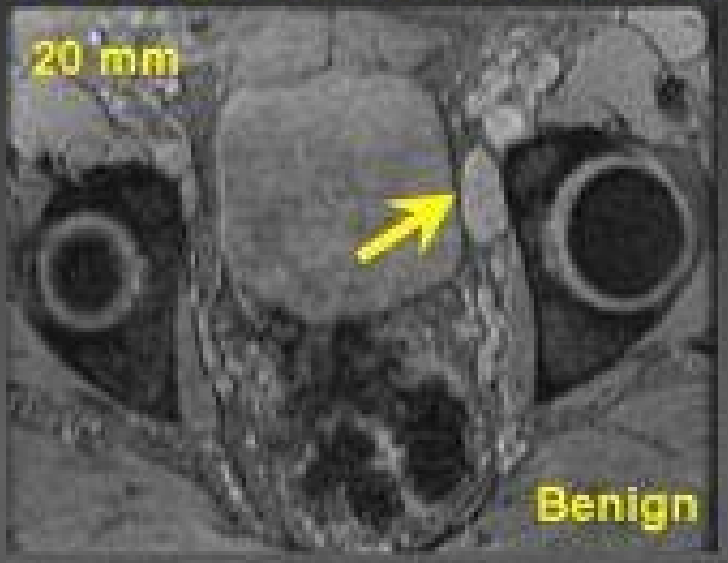
Obturator-hypogastric – 30-60 %
External Iliac – 20-50 %
Both – 37 %

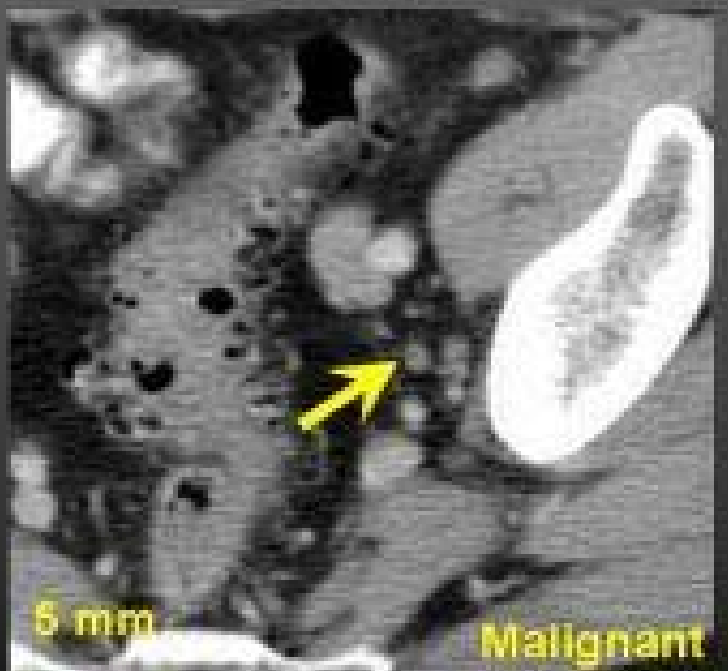
Swanson et al; Cancer 2006; 107; 439

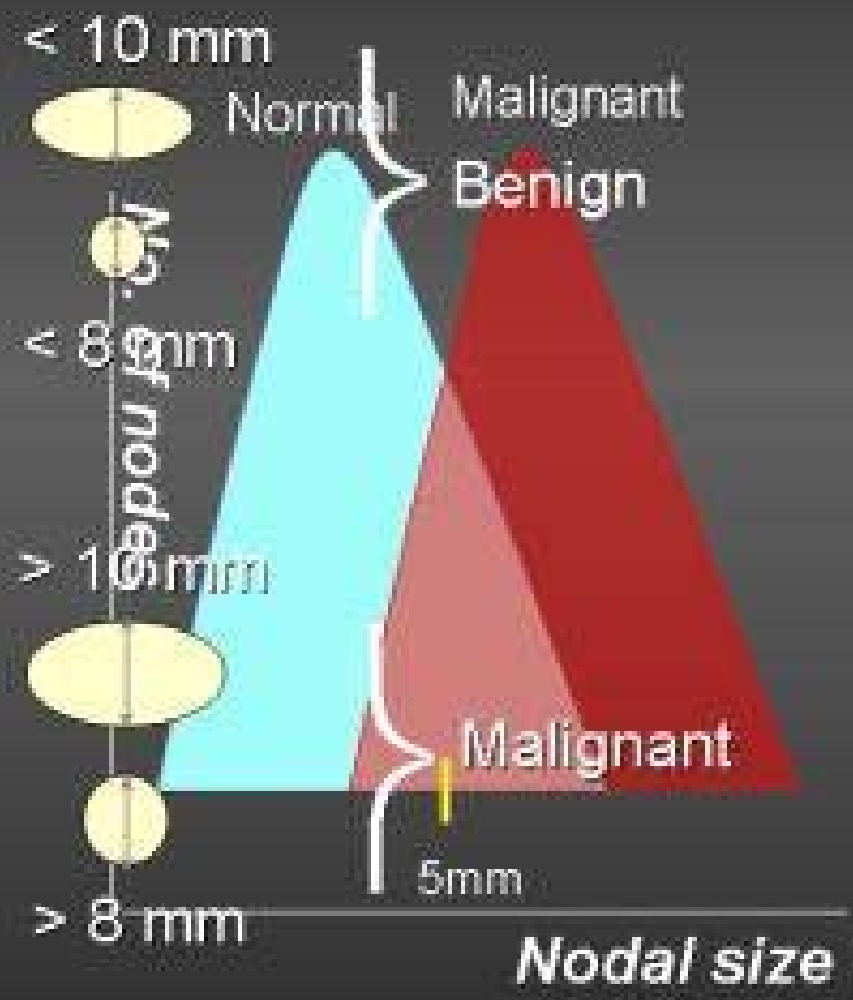
Current Nodal Staging

- Non Invasive
  - Cross Sectional Imaging
- Invasive
  - Surgical Nodal Sampling (Gold Standard)

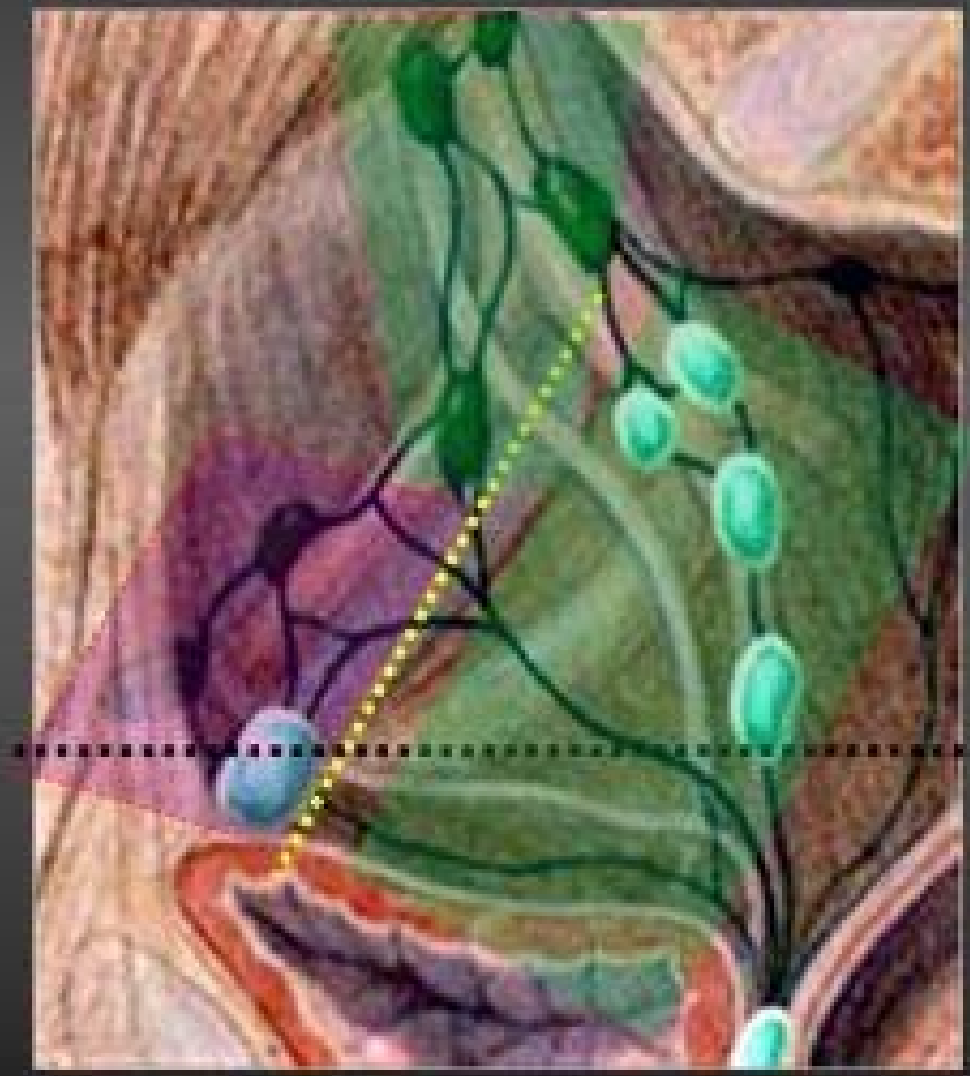
Nodal Characterization

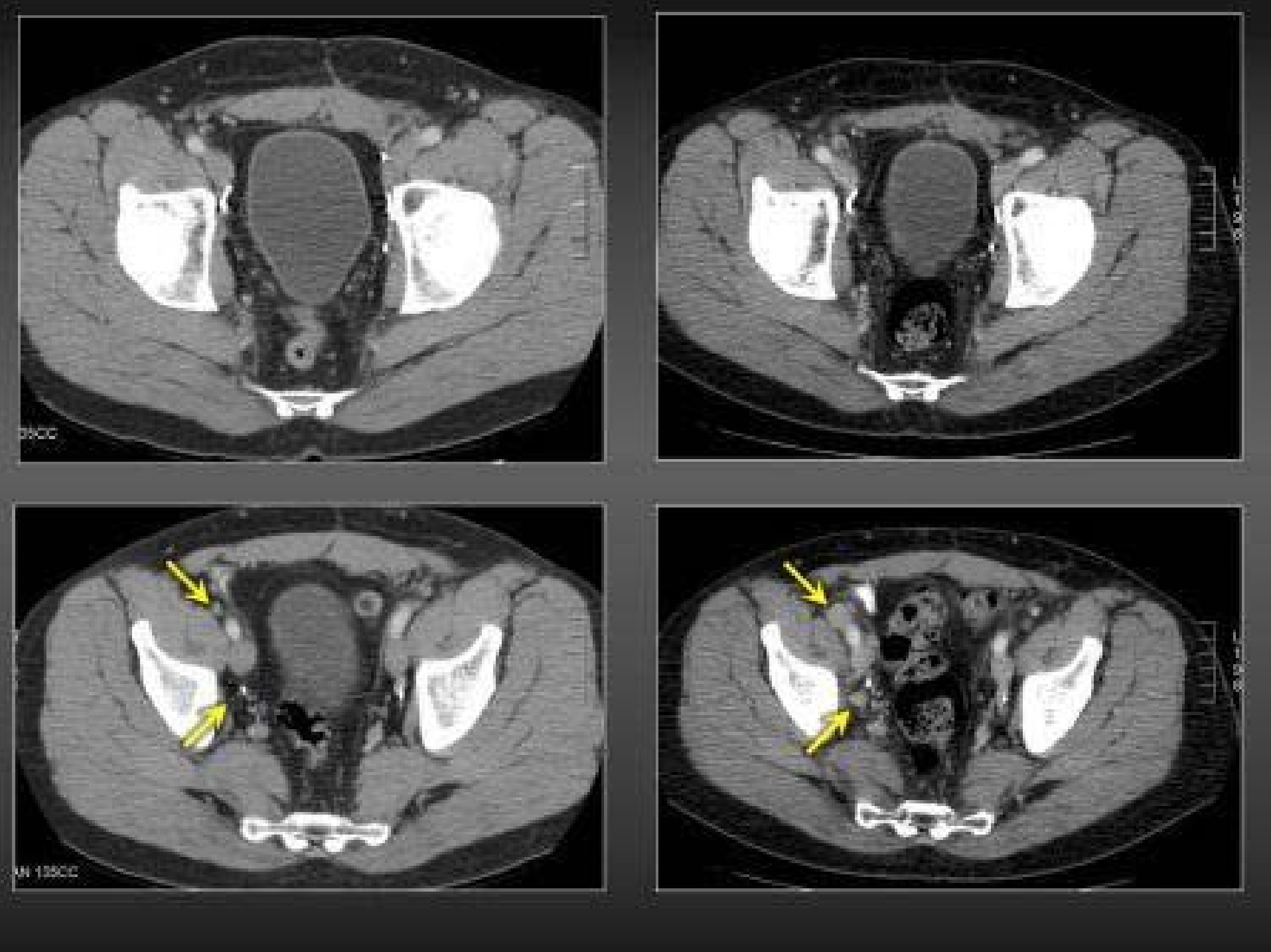




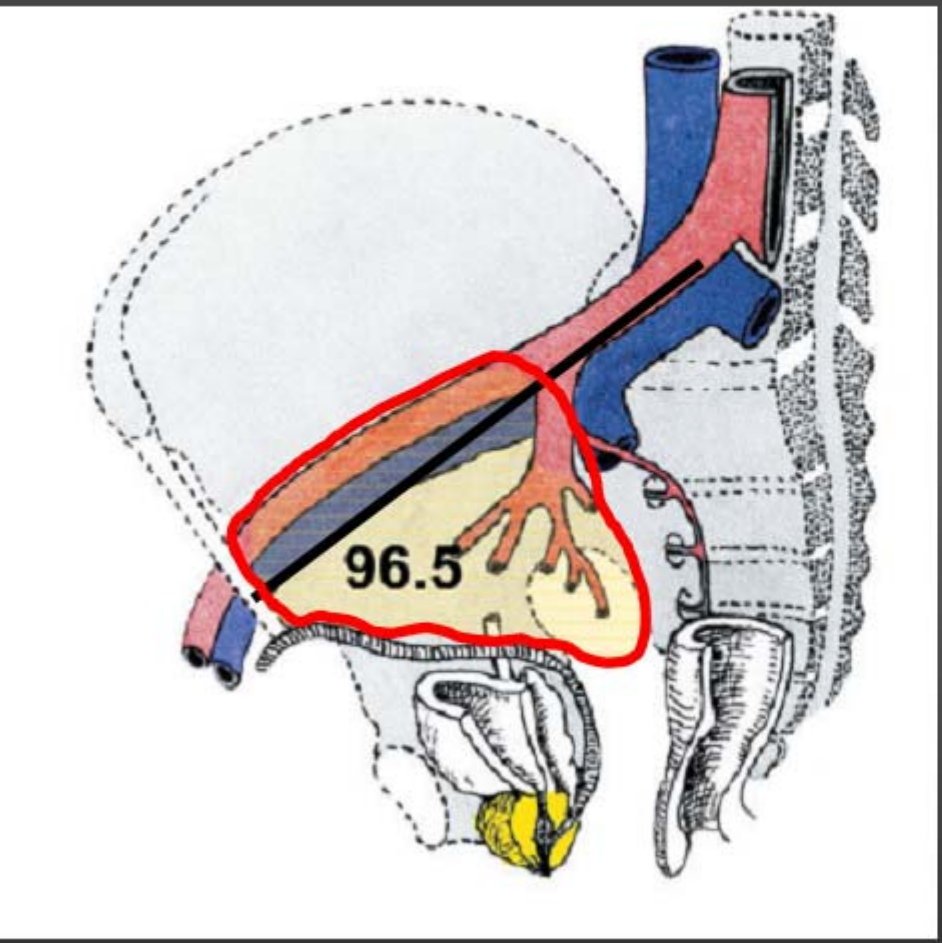


Gold Standard





Extended Surgical Nodal Dissection



Extended pelvic lymphadenectomy

- Incidence of lymph node metastases increased from 10 % to 26.2 %

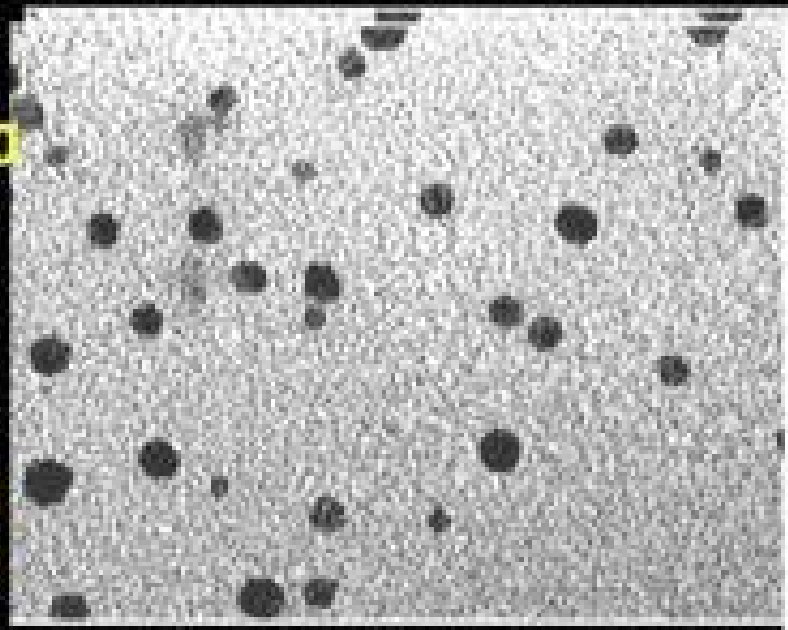
Heidenreich et al. J Urology; April 2002

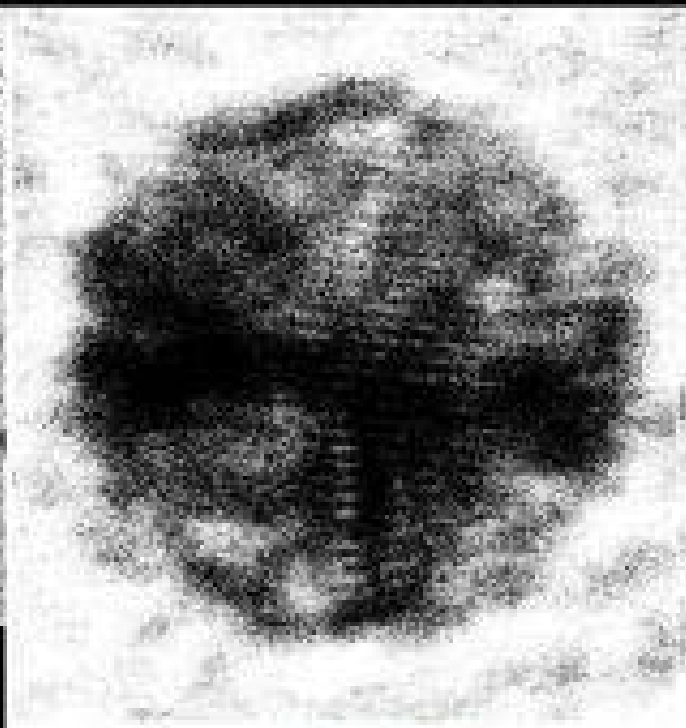
Current Need

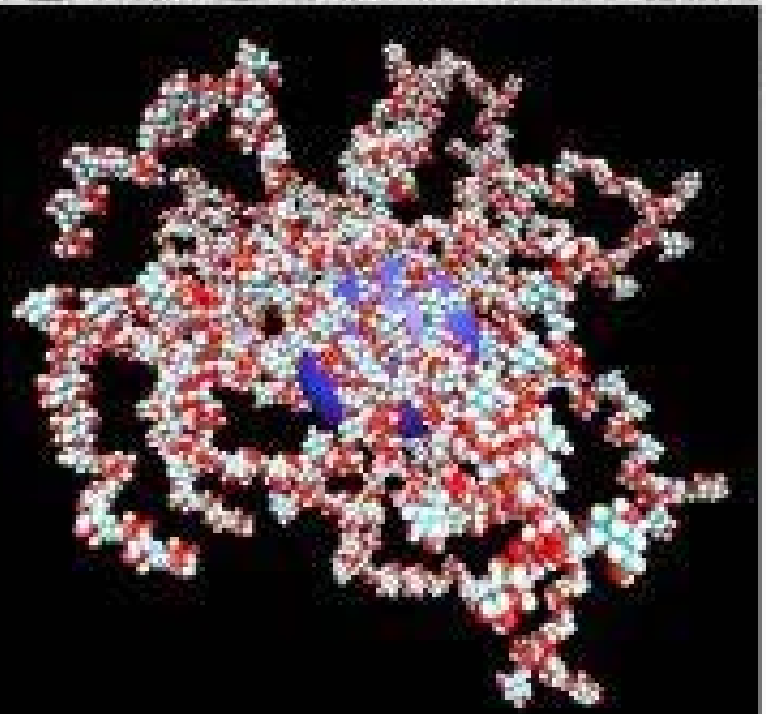
- Non invasive technique that detects, characterized nodes with high degree of sensitivity and specificity
- Broad anatomic coverage for all LN

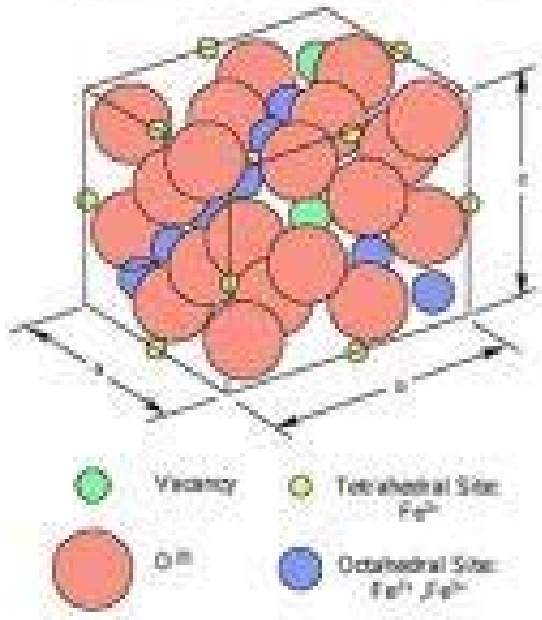
Nanoparticles
Ferumoxtran-10
(Combidex)-
LNMRI

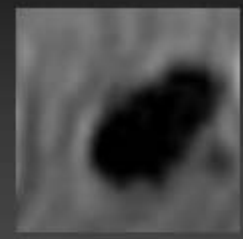
Size: 21 nm
R1: 17 mMsec-1
R2: 48 mMsec-1

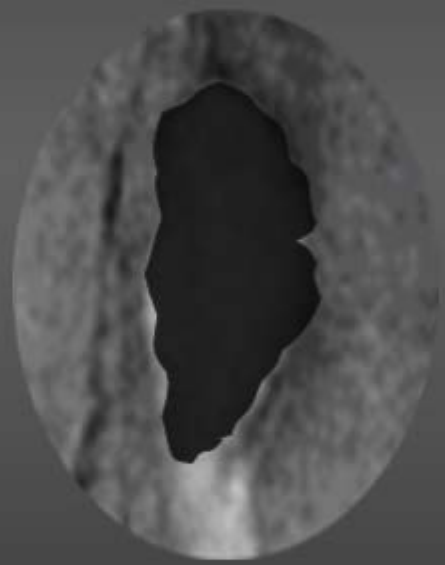




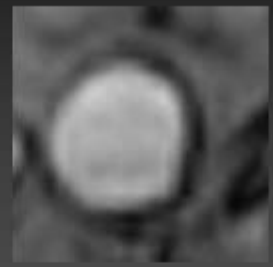


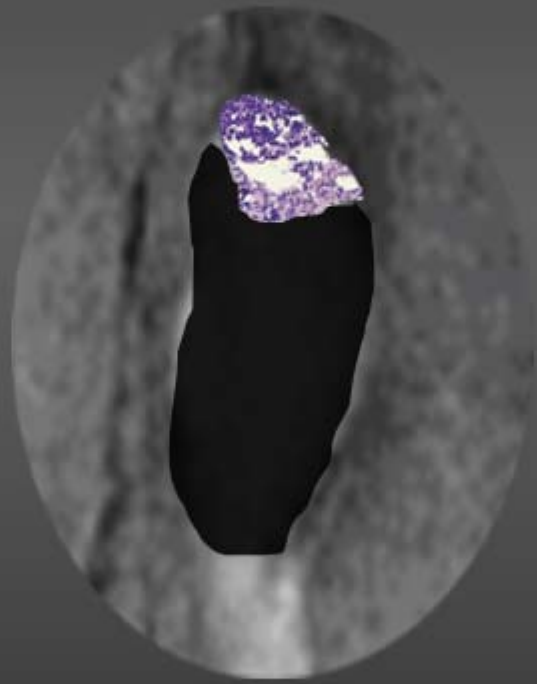






Lymph Node





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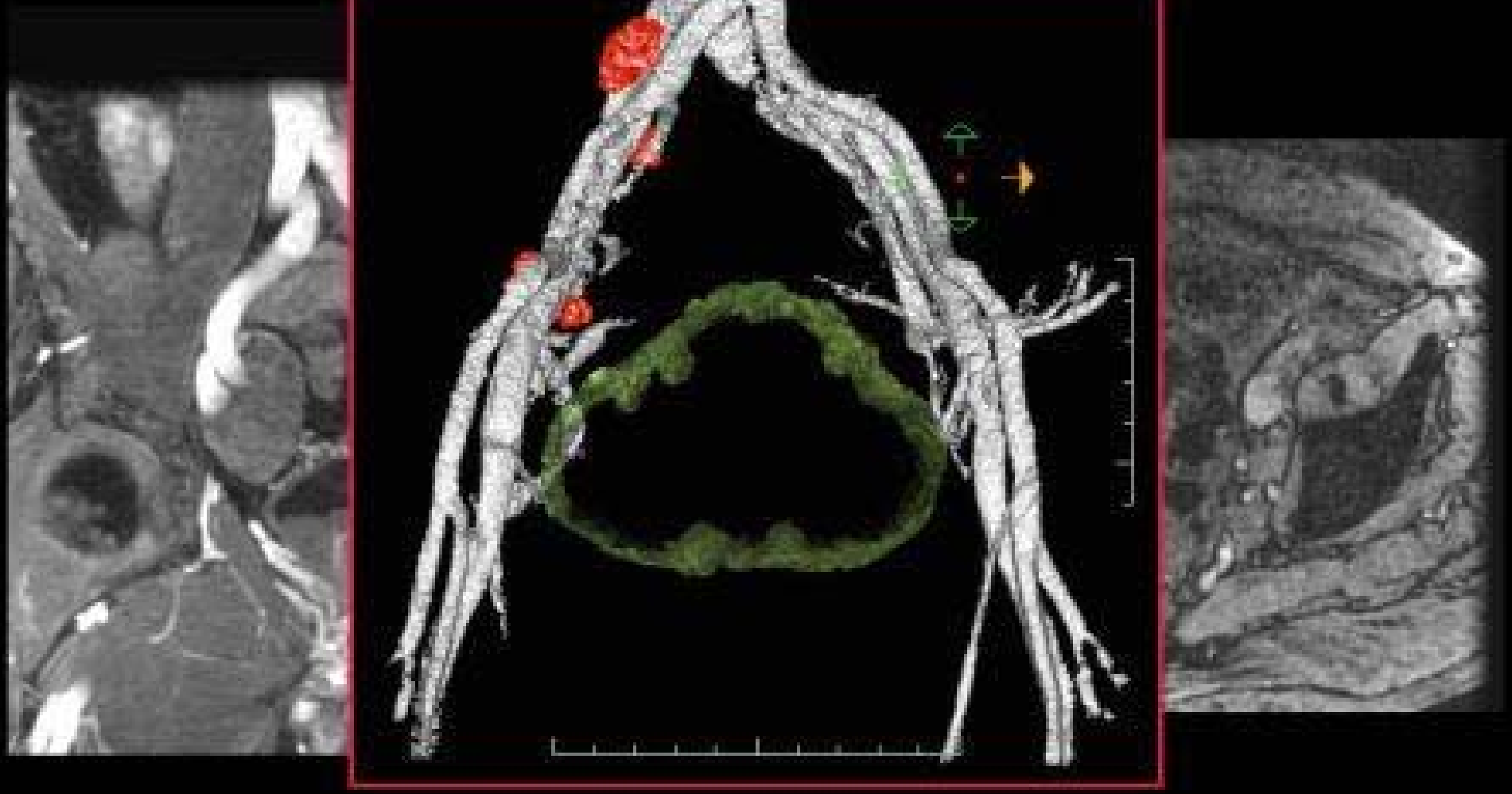
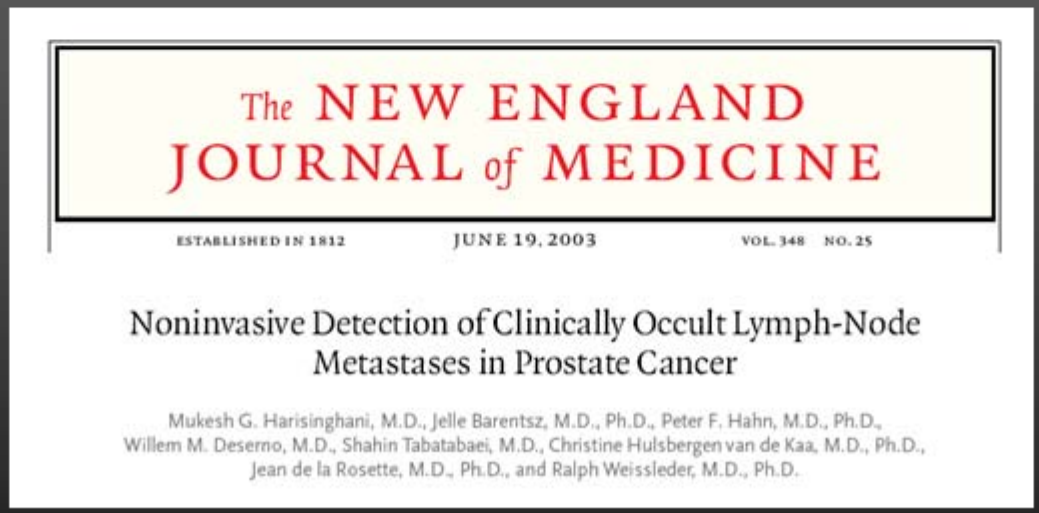


- n = 80 patients (T1 – T3 prostate cancer)
- Lymphotrophic Nanoparticle Enhanced MRI (LNMRI) prior to surgery
- Direct comparison of imaging and histopathology results



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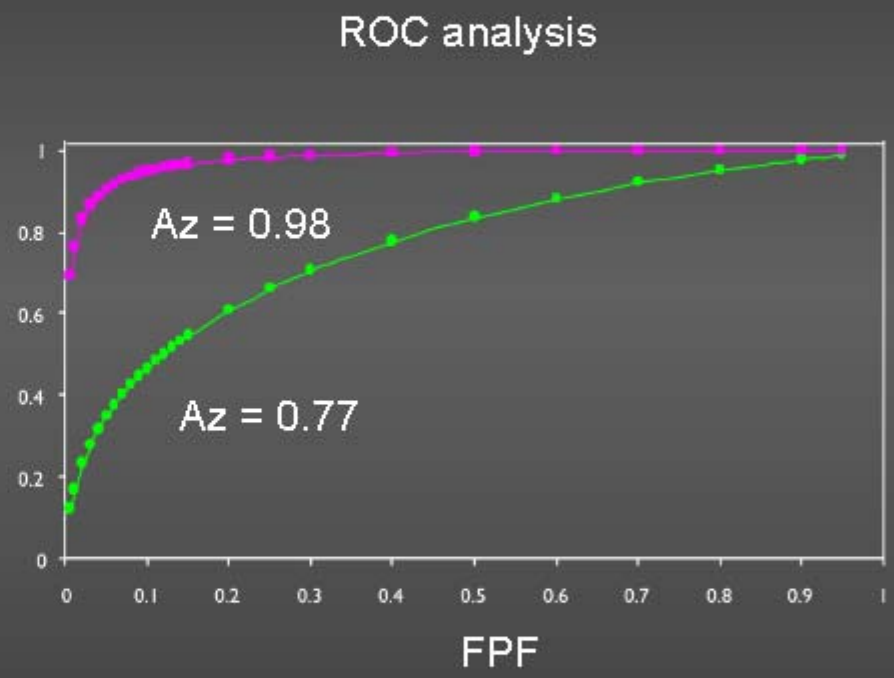
Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer

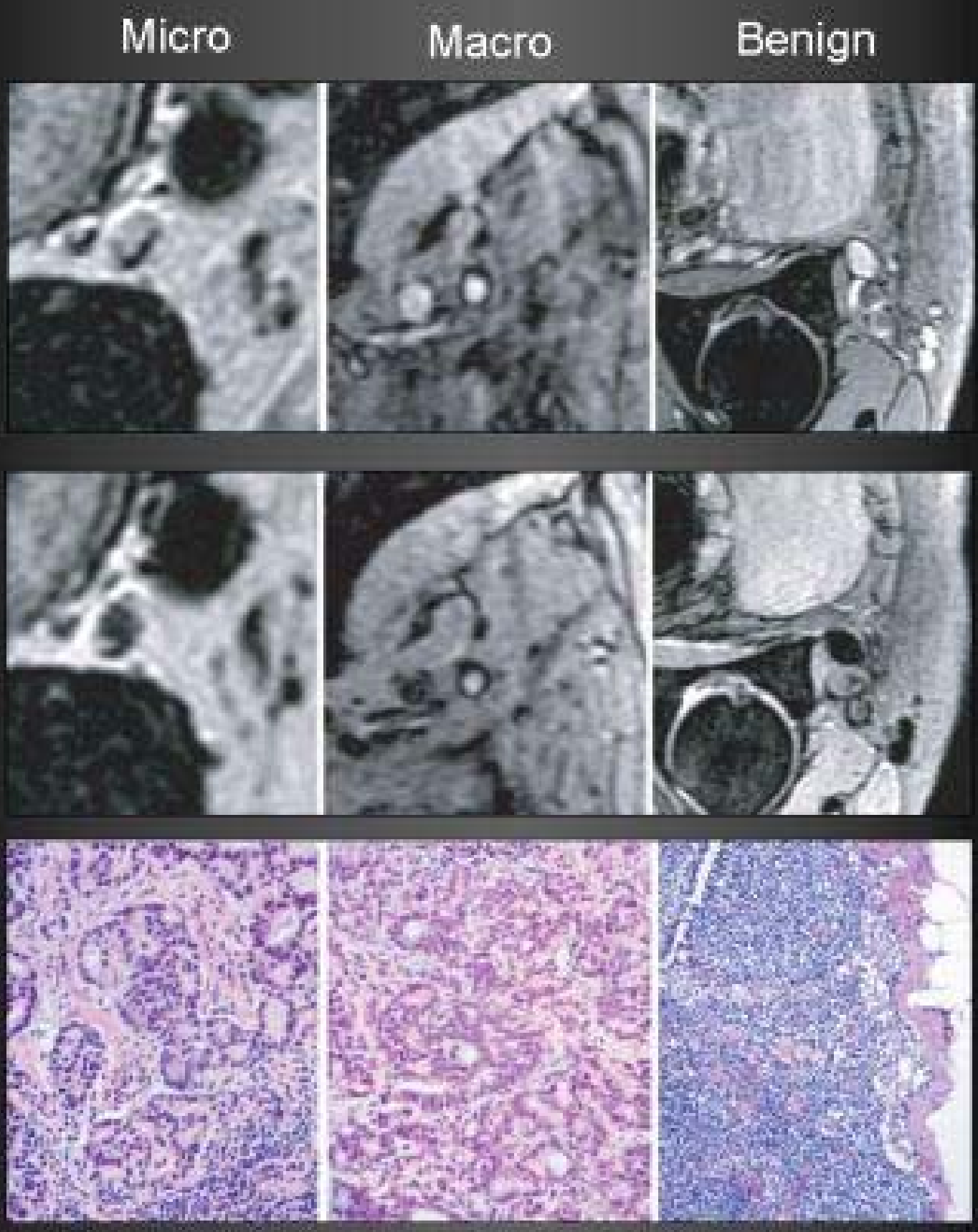
Mukesh G. Harisinghani, M.D., Jelle Barentsz, M.D., Ph.D., Peter F. Hahn, M.D., Ph.D., Willem M. Deserno, M.D., Shahin Tabatabaei, M.D., Christine Hulsbergen van de Kaa, M.D., Ph.D., Jean de la Rosette, M.D., Ph.D., and Ralph Weissleder, M.D., Ph.D.

Results-LNMRI

Accuracy	97%
Sensitivity	92%
Specificity	93%
Negative Predictive Value	97%
Positive predictive Value	95%

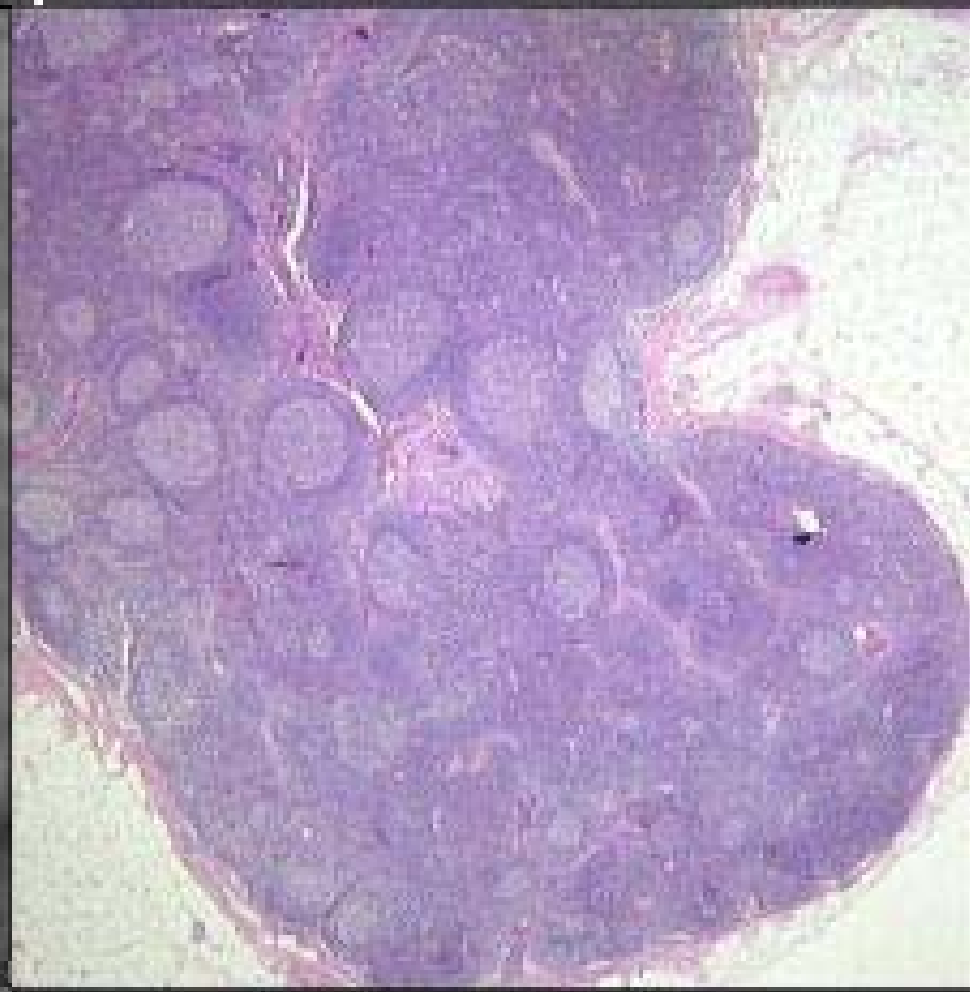


71% of malignant nodes did not meet size criterion for malignancy


Micro
Macro
Benign

LNMRI: Micro-metastasis

post ferumoxtran-10



Effects of LNMRI on patients with prostate cancer

- Staging and Surgical sampling
- Radiation therapy planning
- Response to therapy and recurrence detection

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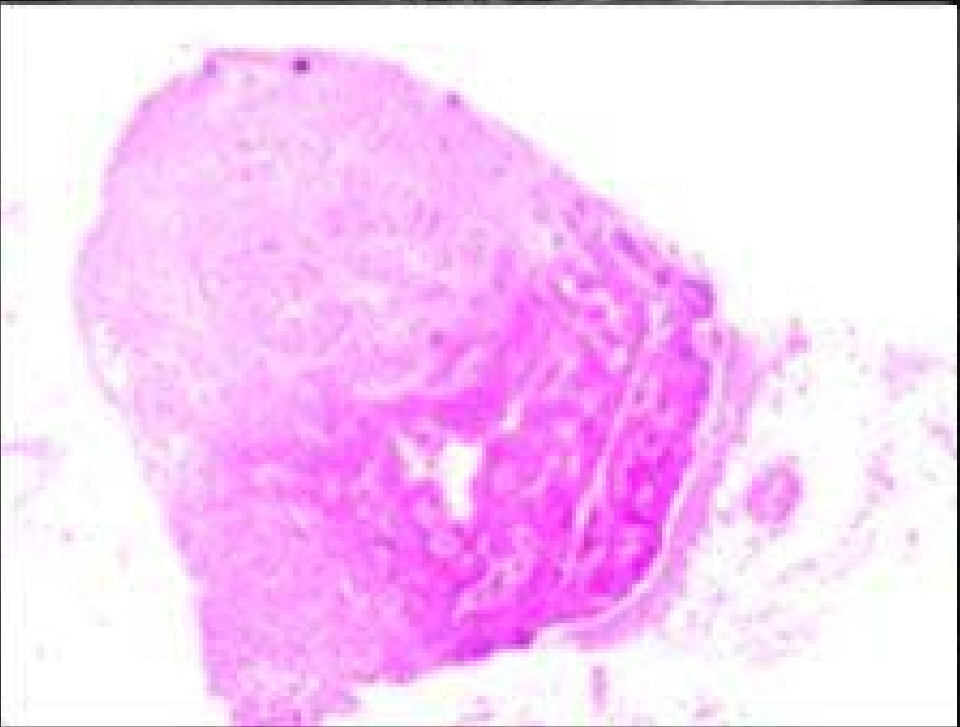
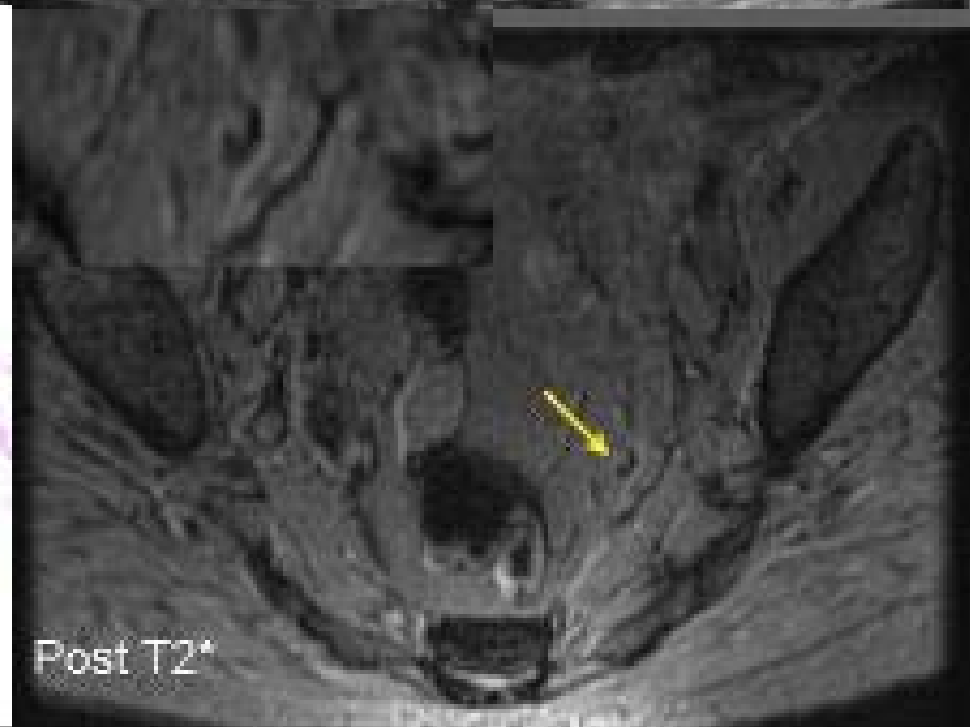
Pre T2

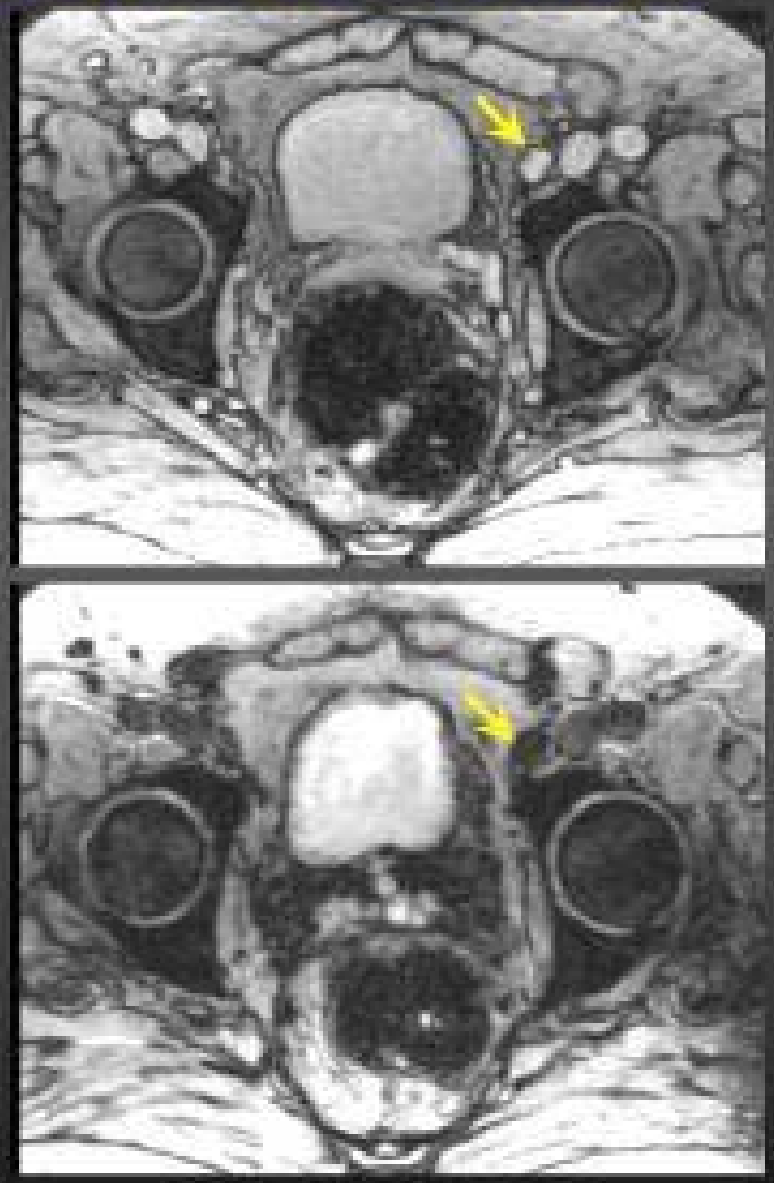
Pre T2*




Post T2*

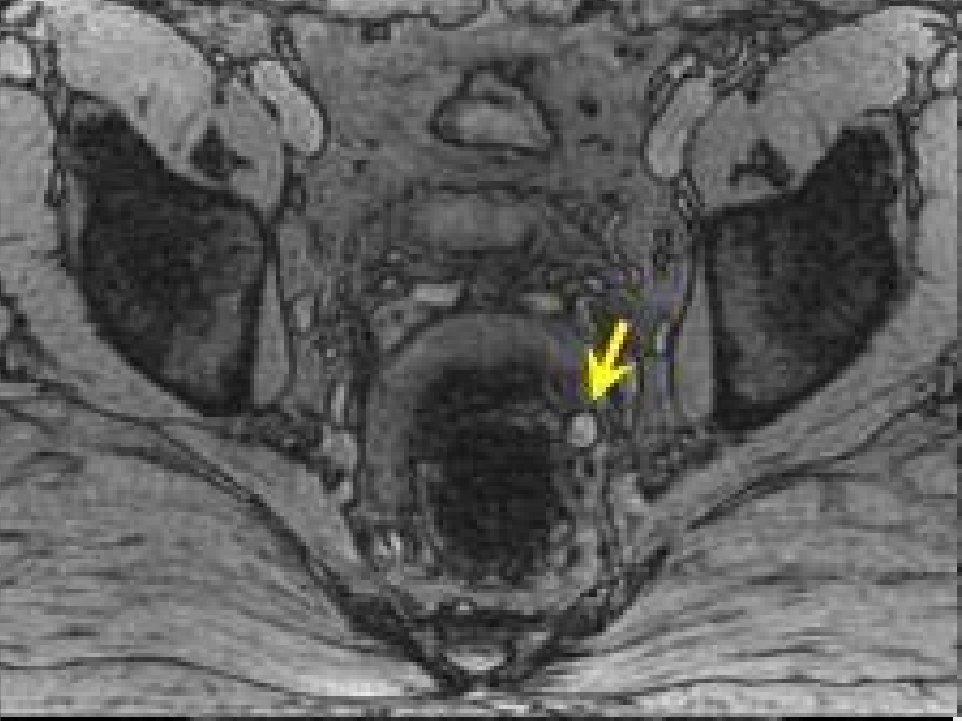
Patient with Prostate Cancer

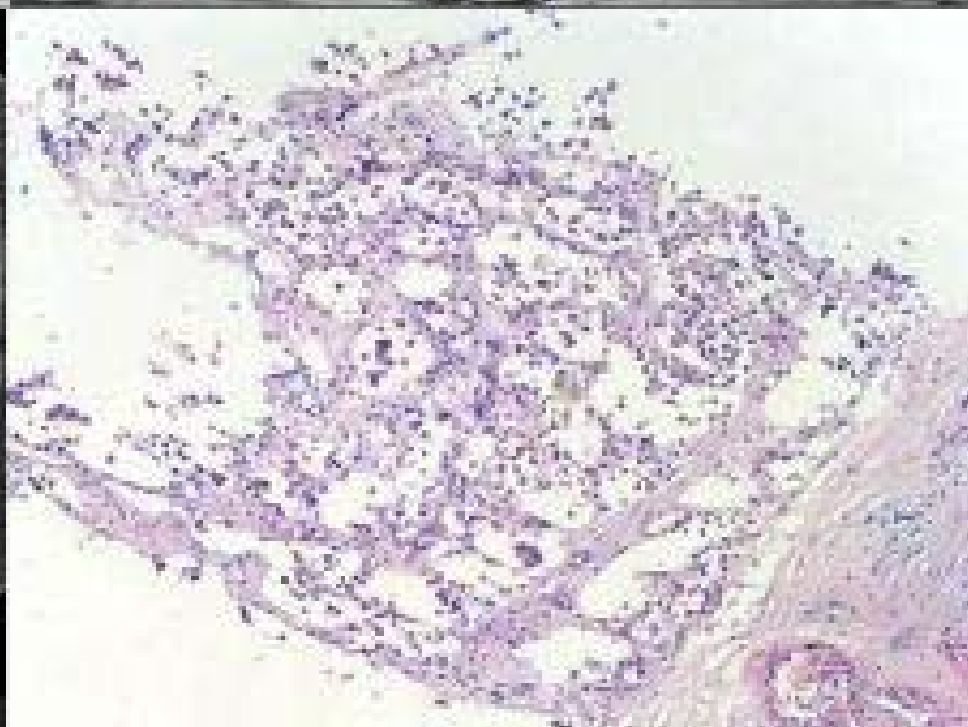
- Negative LNMRI (NPV > 95%)
  - Nodal dissection can be avoided



Patient with Prostate Cancer

- Positive LNMRI with small (< 5 mm) lymph nodes
  - Image guided biopsy





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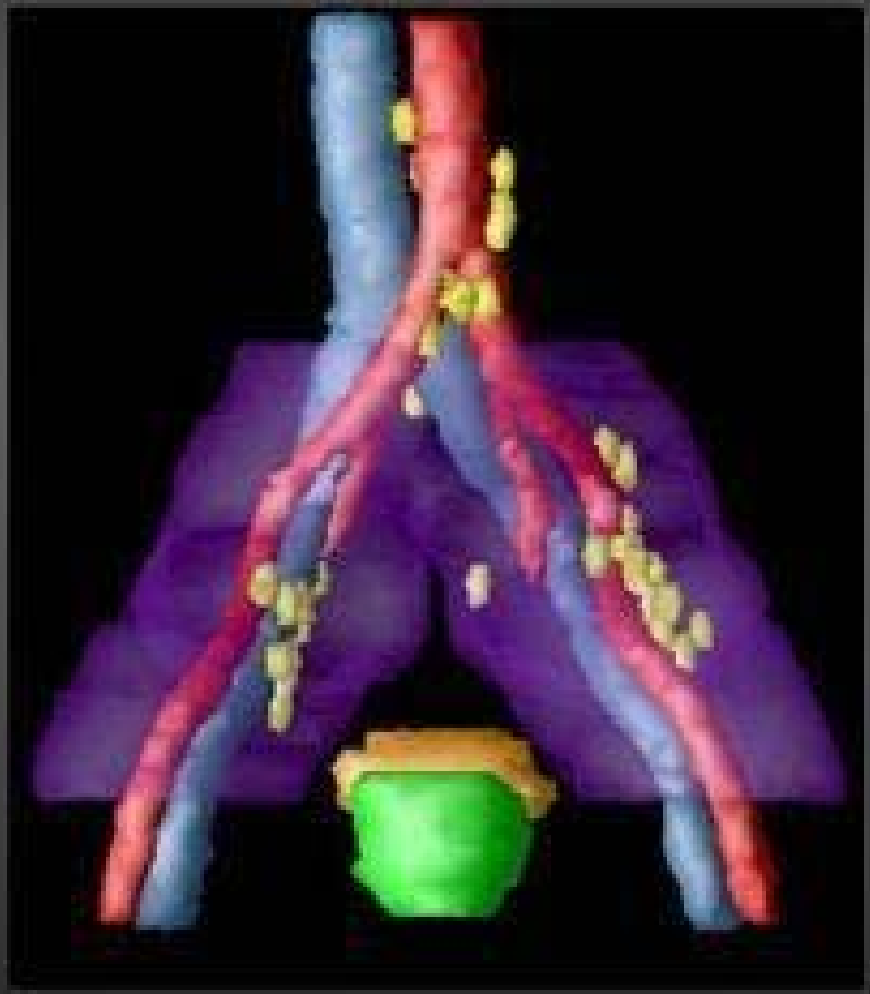
Target Definition

RTOG 9413. *J Clin Oncol* **2003**;21:1904-1911

IMRT planning



IMRT planning

Shih et al; Int J Radiat Oncol Biol Phys 2005; 63:1262

Effects of LNMRI on patients with prostate cancer

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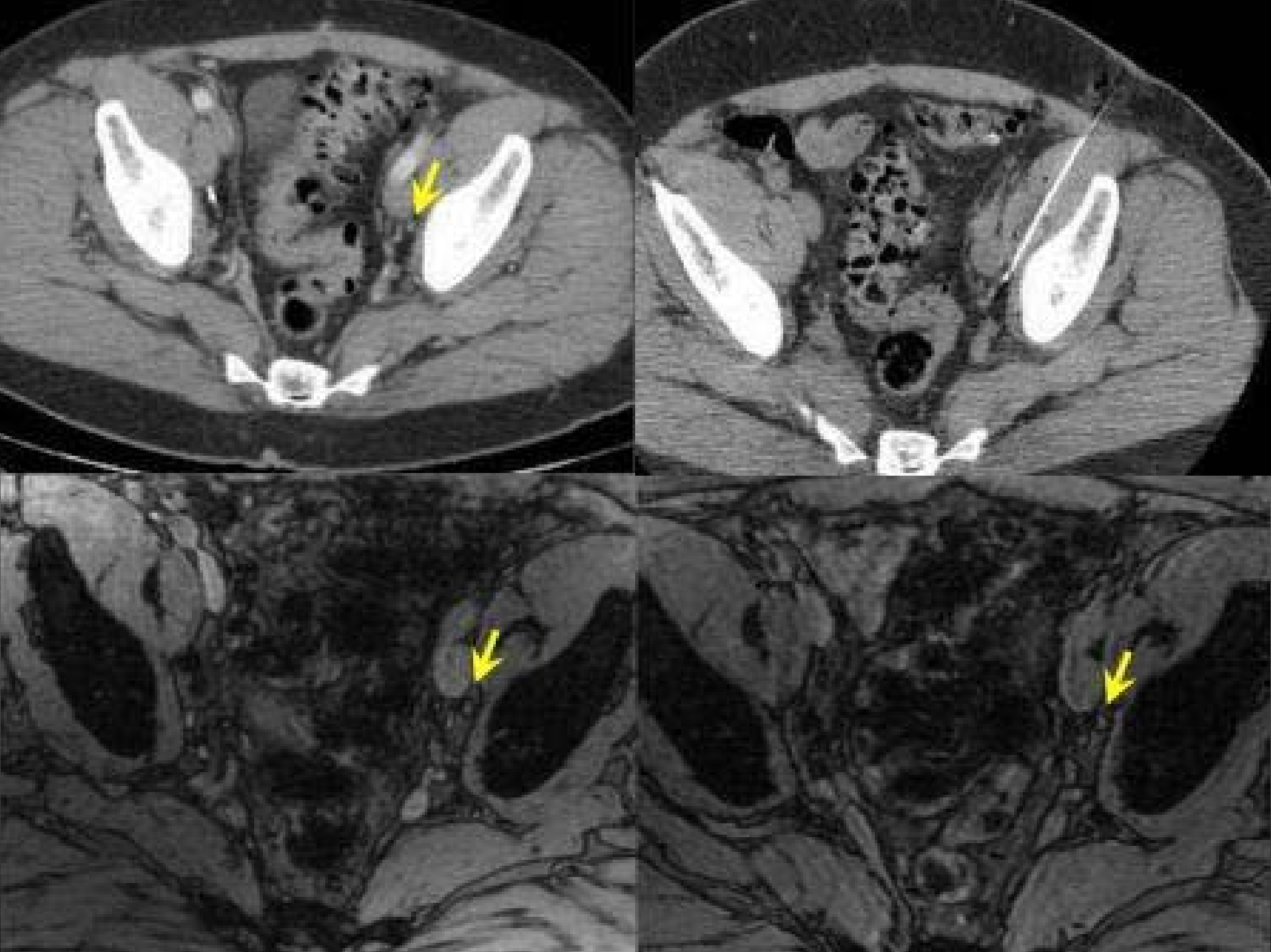


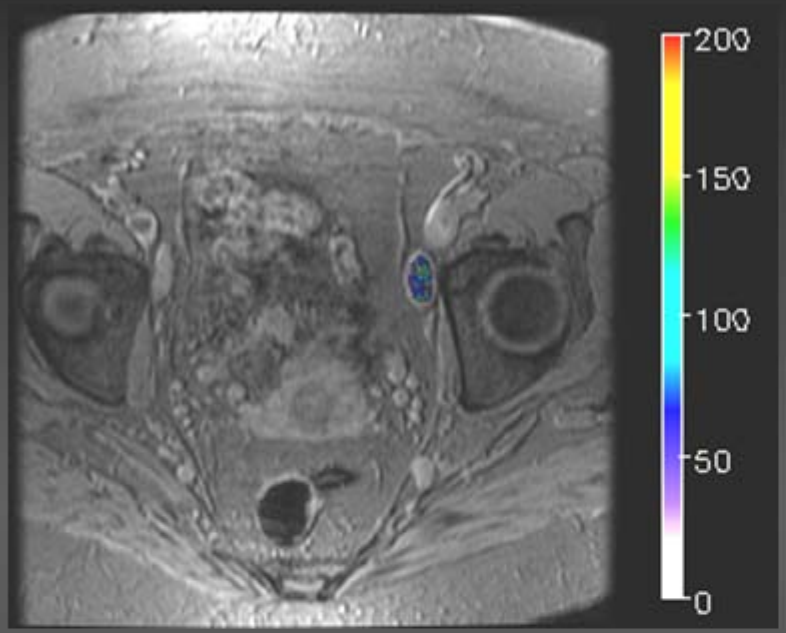
Who should get LNMRI

- Stratify patients with intermediate to high risk of nodal metastases
- Incorporate Partins Nomograms to MRI findings to better predict risk of nodal metastases

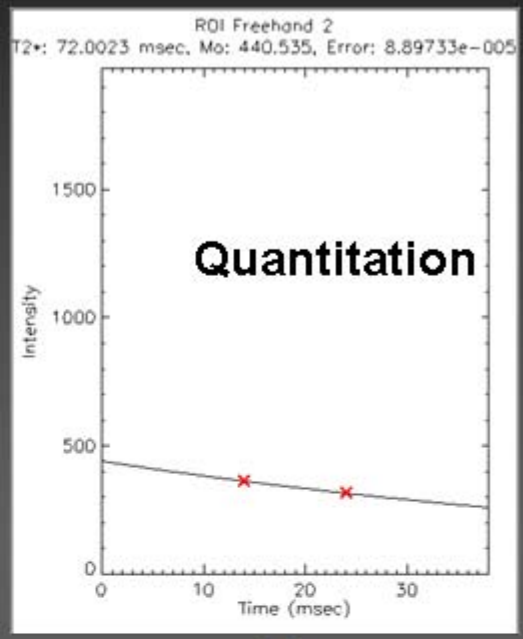
Wang et al; AJR 2006

3T: small nodes

Analysis Enhancement

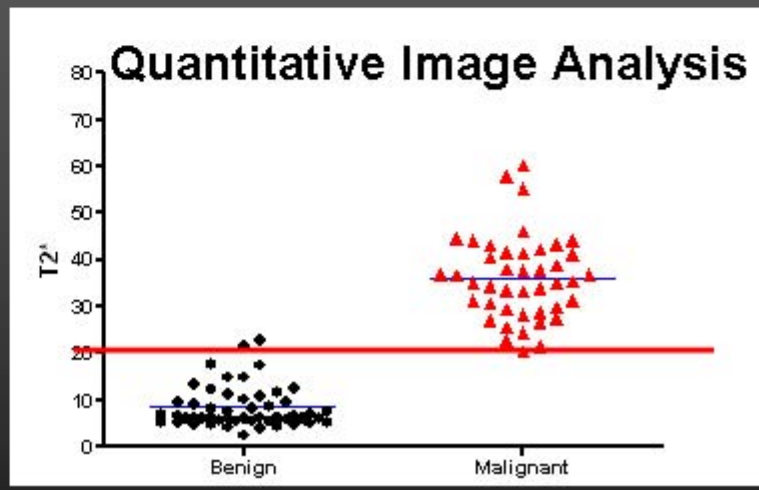


Recognition and Segmentation

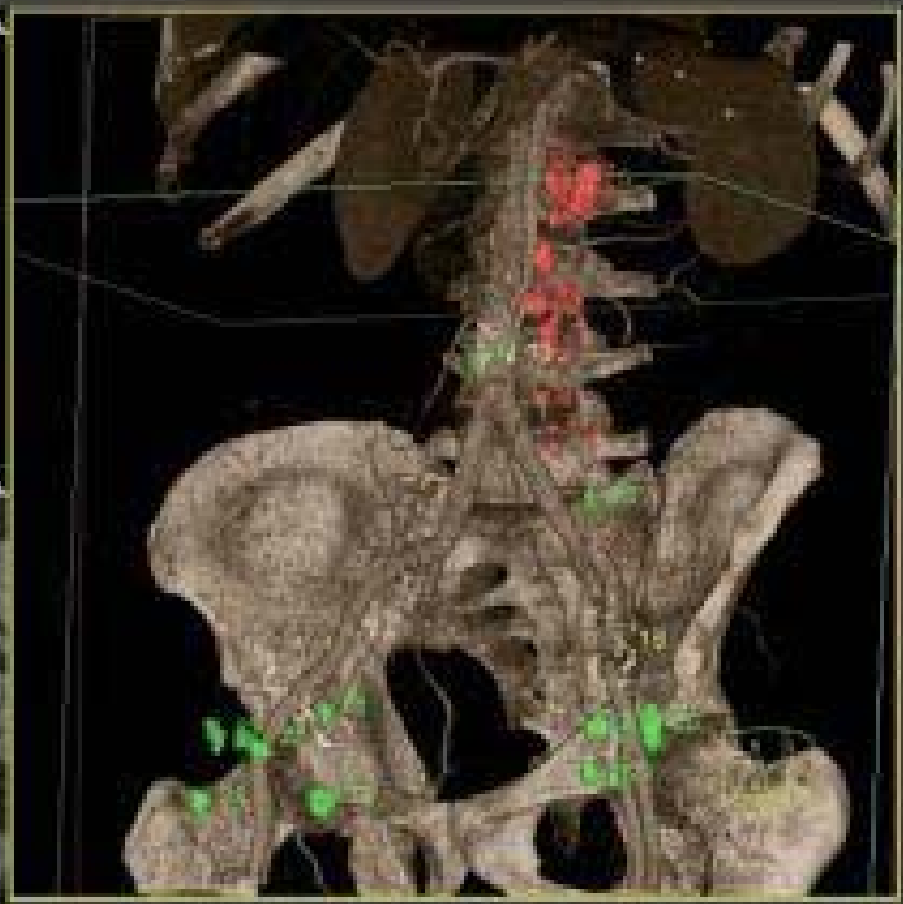


Diagnosis and 3D Rendering

Harisinghani, Weissleder; PLOS Dec 2004



Semi Automated Algorithms



LNMRI Results

Meta-analysis

- **Overall sensitivity 88% (85-91%)**
- **Overall specificity 96% (95-97%)**

LNMRI offers higher diagnostic precision than unenhanced MRI

Will et al Lancet Oncology 2006

Conclusion

- Overall decline in incidence of nodal metastases does not reflect occurrence in high risk patients
- LN staging is crucial for therapy planning and prognostic assessment in prostate cancer patients
- Current imaging techniques and gold standard have limitations
- Need for more accurate techniques to complement surgical staging
  - LNMRI