SCUOLA di URONCOLOGIA

TUMORE della PROSTATA

12 • 13 SETTEMBRE 2014

ROMA

HOTEL SHERATON GOLF
PARCO DE’ MEDICI

V.le Rebecchini, 145

DIAGNOSI E STADIAZIONE
DEL CARCINOMA PROSTATICO

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Persistently Elevated PSA and Negative Prostatic Biopsies (multiple sets): Which Strategy?

* Follow-up with PSA and DRE every 6 months

* Repeat biopsy (Saturation or Template)

* Multiparametric –MRI and targeted biopsies

* -2-Pro-PSA, PCA3……
Case I

Patient 59 y-old. No familiarity for Pca. PS= 0
DRE: Prostate of 30cc. No induration or suspicious area
In 2009 Psa was 6.8 ng/ml. P biopsy (8 cores) : BPH + CP.
In 2011 Psa : 8.05 ng/ml. Biopsy: (12 core) : BPH + CP + HGPIN
What do you suggest?

a. Re-check PSA
b. Re-biopy (Saturation vs Template)
c. Control patient with PSA
d. others
Repeat Biopsy: Indications (2014 EAU Guidelines)

- Rising or persistently elevated PSA
- Suspicious DRE
- Atypical Small Acinar Proliferation (ASAP)
- High Grade PIN (at 1-3 years)

Note: Consider the Pca risk of your patient (familiarity, Psa value, velocity, doubling time, ASAP, HGPIN)
Repeat Biopsies: How

- **Saturation biopsy** (24-30 cores): the incidence of Pca detected by saturation repeat biopsy is 30% - 43% and depends on the N of cores sampled during earlier biopsies.

- **Template biopsy**: (personal experience) 1.5 core x cc of prostate tissue. Detection rate: 50%
  
Always: before focal therapy, AS and ASAP
Repeat Biopsy

If clinical suspicious Cancer persists (+DRE) with negative prostate biopsy M-MRI should be used to evaluate the anterior part of the gland.

In case of suspicious or positive finding: targeted biopsy (US Fusion): if negative follow the patient with PSA.
The Fate of Patients with Elevated PSA who Received Multiple Sets of Prostate Biopsies: Long term Follow-up (Brausi et al Eur Urol 2010)

Material and Methods:
51 pts. with P. elevated PSA
Mean PSA = 8.5 ng/ml (3.3-13.6 ng/ml)
Mean N Sets of biopsies: 2.6 (8-24 cores)
I-PSS: (5-14) = 45/51. (>21) = 6/51
Hystology: BPH = 31/51
BPH + chronic prostatitis = 16/51
BPH + LGPIN = 4/51
Mean Follow-up = 8.2 years (Psa and biopsy if indicated)
Results

- 65% of patients received a 3rd (18) or 4th (12) sets of biopsies for > PSA (> 1 ng/ml in 1 year)
- Histology:
  3 sets: BPH: 10 pts. BPH + chronic prostatitis: 8
  4 sets: BPH: 6 pts. BPH + chronic prostatitis: 3
- Conclusions: 3/51 pts. (6%) with a persistent elevated PSA after neg. multiple sets of biopsies developed PCA in time
D: What to do in case of persistently elevated PSA and negative biopsy?

Answer:
Evaluate the patient risk (familiarity, ASAP, HGPIN, ER (suspicious/no) N of core biopsies previously performed)
Psa velocity o doubling time is important
MRI + US fusion biopsy the best option whe decide to biopsy
In Low risk patients: control with PSA every 6 mos
Quale parametri possono essere considerati predittivi del N?
7.2 N-staging

The gold standard for N-staging is operative lymphadenectomy, either by open or laparoscopic techniques. It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes, and pelvic lymph node dissection that is limited to the obturator fossa will therefore miss about 50% of lymph node metastases (47,48). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered, despite its disadvantages: it requires surgical experience; it is time-consuming; and it often leads to more complications than the limited procedures. Furthermore, it may fail to identify lymph node metastases, however present, even outside the region of extended dissection (49).
Qual’e’ il ruolo della linfadenectomia nella RP

Stadiante  Terapeutica
9.6.4 Conclusions extended lymph node dissection

Extended LND may play a role in the treatment of a subset of intermediate-risk cases with > 5% nomogram predicted risk of positive lymph nodes, and in all high-risk cases.

Extended LND may increase staging accuracy and influence decision making with respect to adjuvant therapy. The number of lymph nodes removed correlates with time to progression.

Surgical morbidity must be balanced against the therapeutic effects, and decisions need to be made based on an individual cases.
N-staging should be performed only when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and peri-neural tumour invasion have been associated with a higher risk of the presence of nodal metastases (3,36,37). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

The nomograms could be used to define a group of patients with a low risk of nodal metastasis, i.e. < 10% (38). In such cases, patients with a serum PSA level of less than 20 ng/mL, stage T2a or less, and a Gleason score of 6 or less may be spared N-staging procedures before potentially curative treatment (3).

The extent of the Gleason 4 pattern in sextant biopsies has also been used to define the risk of N1 disease. If any core had a predominant Gleason 4 pattern, or > three cores any Gleason 4 pattern, the risk of nodal metastases was found to be 20-45%. For the remaining patients, the risk was 2.5%, supporting the idea that nodal staging is unnecessary in selected patients (39).
CONCLUSIONS
Our findings represent the first head-to-head comparison of LNI prediction ability of the NCCN guidelines nomogram, Partin tables, and D’Amico risk-classification. Our study was based on a large population-based cohort of patients treated with RP and PLND. In consequence, our results represent how the examined tools would really perform in everyday practice. The NCCN LNI nomogram had the highest discrimination accuracy. However, using the decision curve analysis, the Partin tables demonstrated the highest net benefit when a threshold probability of LNI is <4%. In contrast, the NCCN LNI nomogram had the highest net benefit when the threshold probability used to perform PLND is >4%.
5. Conclusions

We updated and internally validated the most accurate nomogram (AUC: 87.6%) predicting the probability of LNI in patients undergoing ePLND at RP. It is based on readily and routinely available clinical parameters, such as PSA, clinical stage, biopsy Gleason sum, and percentage of positive cores. Among these, the percentage of positive cores represents the foremost predictor of LNI and should be included in any LNI prediction model. Using a 5% nomogram cut-off, roughly two-thirds of patients would be spared ePLND, and LNI would be missed in only 1.5%. Therefore, in the absence of prospective data supporting the role of ePLND in PCa outcome, ePLND might be safely omitted in all patients with a nomogram-derived LNI risk <5%.
Altre Indagini Nella Diagnosi Di N+

- CT
- MRI (High resolution- USPIO)
- CT-PET Colina
- Sentinel Node
In the current published literature, the results indicate that CT and MRI perform similarly in the detection of pelvic lymph node metastases, although CT seems to be slightly superior (40) (LE: 2a). In either case, the decision about whether nodal involvement is present rests solely on whether there is enlargement of the investigated lymph nodes. A threshold of 1 cm in the short axis for the oval nodes, and 0.8 cm for the round nodes, has been recommended as the criteria for the diagnosis of lymph node metastases (41).

A fine-needle aspiration biopsy (FNAB) might provide a decisive answer in cases of positive imaging results. However, the lymph node can be difficult to reach because of the anatomical position. In addition, FNAB is not a highly sensitive staging procedure, and a false-negative rate of 40% has been reported (41).

High-resolution MRI with lymphotrophic ultra-small super-paramagnetic iron oxide particles (USPIO) was more recently suggested in the detection of small and otherwise occult lymph node metastases in patients with PCa (42,43).

In asymptomatic patients with newly diagnosed PCa and a serum PSA level of less than 20 ng/mL, the likelihood of positive findings on CT or MRI is approximately 1% (32). CT scanning may therefore be warranted in patients with a very high risk of harbouring lymph node metastases, as the specificity of a positive scan is
Ultrasmall superparamagnetic particles of iron oxide allow for the detection of metastases in normal sized pelvic lymph nodes of patients with bladder and/or prostate cancer.

Maria Triantafyllou, Urs E. Studer, Frédéric D. Birkhäuser, Achim Fleischmann, Lauren J. Bains, Giuseppe Petralia, Andreas Christie, Johannes M. Froehlich, Harriet C. Thoeny

Fig. 2. Typical example of ultrasmall superparamagnetic particles of iron oxide (USPIO) uptake in positive and negative lymph nodes. Axial T2w-reconstructed images before (A) and after (B) the administration of USPIO in a 67-year-old prostate cancer patient. The benign lymph node (black arrow) shows a decrease in signal intensity after the uptake of USPIO; the malignant lymph node (white arrow) shows only partial posterior and medial signal decrease after the administration of USPIO.
Platinum Priority – Prostate Cancer and Bladder Cancer

Combined Ultrasmall Superparamagnetic Particles of Iron Oxide–Enhanced and Diffusion-Weighted Magnetic Resonance Imaging Reliably Detect Pelvic Lymph Node Metastases in Normal-Sized Nodes of Bladder and Prostate Cancer Patients

Harriet C. Thoeny a, Maria Triantafyllou a, Frederic D. Birkhaeuser b, Johannes M. Froehlich c, Dechen W. Tshering a, Tobias Binser d, Achim Fleischmann e, Peter Vermathen d, Urs F. Studer b, e

Table 1 – Comparison of the diagnostic accuracies for the classic reading method a versus the new USPIO-DW-MRI reading method b with regard to histopathology

<table>
<thead>
<tr>
<th>Readings</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>Classic per patient</td>
<td>0.80</td>
<td>0.73</td>
<td>0.90</td>
<td>0.50</td>
<td>0.92</td>
</tr>
<tr>
<td>Classic per patient plus DW-MRI</td>
<td>0.80</td>
<td>0.87</td>
<td>0.90</td>
<td>0.67</td>
<td>0.93</td>
</tr>
<tr>
<td>Classic per pelvic side plus DW-MRI</td>
<td>0.71</td>
<td>0.94</td>
<td>0.90</td>
<td>0.71</td>
<td>0.94</td>
</tr>
<tr>
<td>New USPIO-DW-MRI per patient reader 1</td>
<td>0.80</td>
<td>0.93</td>
<td>0.90</td>
<td>0.80</td>
<td>0.93</td>
</tr>
<tr>
<td>New USPIO-DW-MRI per patient reader 2</td>
<td>0.60</td>
<td>0.80</td>
<td>0.75</td>
<td>0.50</td>
<td>0.86</td>
</tr>
<tr>
<td>New USPIO-DW-MRI per patient reader 3</td>
<td>0.80</td>
<td>0.87</td>
<td>0.85</td>
<td>0.67</td>
<td>0.93</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value.

a First pre- versus post-T2-weighted ultrasmall superparamagnetic particles of iron oxide (USPIO) (two readers; without and with diffusion-weighted magnetic resonance imaging [DW-MRI]).

b First USPIO-DW-MRI (three independent blinded readers) on a per-patient (n = 20) and per-pelvic-side (n = 40) basis.

5. Conclusions

The present results suggest that USPIO-enhanced MRI in combination with DW-MRI is a novel, accurate, and fast method for detecting pelvic lymph node metastases even in normal-sized nodes of patients with bladder or prostate cancer.
Surgery in Motion

Intraoperative Laparoscopic Fluorescence Guidance to the Sentinel Lymph Node in Prostate Cancer Patients: Clinical Proof of Concept of an Integrated Functional Imaging Approach Using a Multimodal Tracer

Henk G. van der Poel, Tessa Buckle, Oscar R. Brouwer, Renato A. Valdés Olmos, Fjis W.B. van Leeuwen

Fig. 1 - Protocol setup. (A) In situ formation of the multimodal radiocolloid that contains both a radioactive and a fluorescent component. (B) (1) Transrectal ultrasound-guided intraprostatic injection of the indocyanine (ICG)99mTc-NanoColloid tracer; (2) preoperative single-photon emission computed tomography/computed tomography (SPECT-CT) arrows indicate sentinel lymph nodes (SLNs); and (3) intraoperative SLN detection using a near infrared (NIR)-laparoscopic Delight angio NIR fluorescence imaging system (screen 1 fluorescence depicted in green). The da Vinci S surgical goggle using the system’s Tile/Pro function were used to simultaneously depict the three-dimensional surgical field and the intraoperative NR-laparoscopic image in blue (blue arrow; II). White circles highlight the fluorescent area.
Conclusions: Initial data indicate that multimodal ICG-$^{99m}$Tc-NanoColloid, in combination with a laparoscopic fluorescence laparoscope, can be used to facilitate and optimize dissection of SLNs during RALP procedures.
Quale Ruolo ha la Pet/Colina?
The role of PET/computed tomography scan in the management of prostate cancer

Maria Picchio\textsuperscript{a,b}, Elisabetta Giovannini\textsuperscript{a} and Cristina Messa\textsuperscript{b,c,d}

**Key points**

- PET/computed tomography (CT) with 11C/18F-choline is clinically recommended in the evaluation of patients with biochemical relapse, for lymph nodal and bone metastases detection.
- PET/CT with 11C/18F-choline is not indicated for the diagnosis and staging of primary PCA.
- PET/CT with 11C-acetate, although promising, is still investigative for pretreatment and post-treatment management of prostate cancer patients.
- PET/CT with 18F-fluoride, although still investigative, could play a clinical role in the detection of malignant skeletal involvement in both pretreatment and post-treatment phase.

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tailored to the patient [11\textsuperscript{**}]. Currently, pelvic lymphadenectomy is the gold standard to assess the status of pelvic lymph nodes, being final diagnosis defined by histology [4]. A diagnostic imaging tool to noninvasively explore patients and to detect metastases would be of particular help in clinical management. In lymph nodal detection, 11C-choline PET/CT specificity has been reported fairly high. However, its sensitivity is not appropriate [33]. A negative 11C-choline PET/CT study does not appear sufficient to rule out a lymphadenectomy [22,32,33]. However, when positive, PET/CT may be useful for patient management and treatment planning [9\textsuperscript{*},32,34]. Although few studies on the use of PET/CT with 11C-acetate in PCA are now available [19,23,32,34–36], its final role in clinical practice has not been conclusively defined.
La scintigrafia ossea: Quando dovrebbe essere eseguita?
Quando effettuare la scintigrafia ossea

- Quali parametri identificano un significativo rischio di metastasi ossea nello staging pretrattamento?

- Quale metodica di imaging identifica meglio una metastasi ossea?
American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: Metastatic Bone Disease

Variant 7: Prostate nodule on physical examination proven to be a well- or moderately differentiated carcinoma and PSA <20 mg/ml. Patient asymptomatic.

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
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<tr>
<td>MRI area of interest without contrast</td>
<td>1</td>
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<td>O</td>
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<tr>
<td>MRI area of interest without and with contrast</td>
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<td>X-ray radiographic survey whole body</td>
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<td>Tc-99m bone scan whole body</td>
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<tr>
<td>FDG-PET/CT skull base to mid-thigh</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level
**Variant 8:** Prostate nodule on physical examination proven to be a poorly differentiated carcinoma or PSA ≥20 mg/ml. Patient asymptomatic.

<table>
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<td>CT area of interest without contrast</td>
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<td>FDG-PET/CT skull base to mid-thigh</td>
<td>1</td>
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<td>4</td>
</tr>
</tbody>
</table>

**Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level*
McArthur et al. (http://www.ncbi.nlm.nih.gov/pubmed/21304009) have just reported data from a cohort of > 800 patients in whom they sought to ensure the feasibility of implementing the

- The entire database included 819 patients, of whom 633 were assessed retrospectively and 186 prospectively.
- 672/819 patients met all the inclusion criteria.
- The average (median) age of the eligible patients was 71 years (range, 39 to 93 years).
- 54/672 eligible patients (8 percent) had evidence of metastasis to bone based on their bone scans.
- PSA levels and Gleason scores were both independent predictors of a positive bone scan, and their predictive value was additive.
- 357/672 patients had a PSA level < 20 ng/ml and a Gleason score < 8 and none of these patients had a positive bone scan.

McArthur et al. very reasonably conclude that a bone scan “can be safely omitted” from the work-up of newly diagnosed prostate cancer patients with a PSA level < 20 ng/ml and a Gleason score < 8.
Unnecessary Imaging for the Staging of Low-risk Prostate Cancer Is Common

Hugh J. Lavery, Jonathan S. Brajtibord, Adam W. Levinson, Fatima Nabizada-Pace, Matthew E. Pollard, and David B. Samadi

Figure 1. Imaging examinations performed on low-risk prostate cancer patients (n = 677).

Figure 2. Radiographic interpretation for lymphadenopathy, bone metastasis, and extracapsular disease on preoperative imaging in low-risk prostate cancer patients.
Clinicians Versus Nomogram: Predicting Future Technetium-99m Bone Scan Positivity in Patients With Rising Prostate-specific Antigen After Radical Prostatectomy for Prostate Cancer

Michael W. Kattan, Changhong Yu, Andrew J. Stephenson, Oliver Sartor, and Bertrand Tombal

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**Figure 1.** Slovin nomogram used to predict patient-specific probabilities of bone scan positivity. Adapted with permission from the American Association for Cancer Research (http://dx.doi.org/10.1158/1078-0432.CCR-05-1668).

bPSA, baseline prostate-specific antigen; PFS, progression-free survival; PSADT, prostate-specific antigen doubling time.
## NOPR Medicare Reimbursement for PET in Prostate Cancer (subject to change)

### Table C

<table>
<thead>
<tr>
<th>Indications</th>
<th>Initial Treatment Strategy (formerly Diagnosis and initial Staging)</th>
<th>Subsequent Treatment Strategy (includes Treatment Monitoring, Restaging and Detection of Suspected Recurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>NC (non-covered nationally – Not eligible for entry in the NOPR)</td>
<td>NOPR (covered only with entry in the NOPR)</td>
</tr>
</tbody>
</table>

### Follow-Up & Additional Bone Imaging

If the physician who read and signed your bone scan report found something that he thought to be suspicious, but not definitive, he may suggest ordering additional imaging to rule out cancer metastasis. You will probably find different clinical opinions on what type of imaging is most useful, or even on when follow-up imaging is necessary. But here are some pointers that can help in your understanding.
Q: Bone Scan: Indications

Answer:
Bone scan is indicated when PSA is > 20 ng/ml, Gleason score 8 and when patients are symptomatic with an elevated Alkaline Phosphatase.
GRAZIE, per ora ......