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The changing role of imaging in clinical care

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Abstract

Considerable developments in prostate cancer in 2013 have emerged from the imaging field. Hyperpolarized ¹³C-MRI can monitor metabolic activity to identify high-grade disease and treatment response, and novel PET radiotracers might identify distinct subsets of patients with advanced disease. These examples highlight the progress made at all stages of care.

Alongside advances in drug development, 2013 has arguably been the year of imaging in prostate cancer. Emerging imaging modalities are now being applied at all points in the disease process—including at initial diagnosis, during active surveillance of localized disease, upon biochemical relapse and in metastatic disease—and are likely to considerably shape practice patterns in years to come.

Current standard practice of diagnosing prostate cancer involves transrectal sampling of 10–14 bilateral cores of prostate cancer tissue. However, a substantial false-negative rate is associated with this approach, especially with lesions in the anterior prostate gland. Multiparametric proton-based (¹H) MRI (mpMRI), using T2, diffusion-weighted, dynamic contrast-enhanced and ¹H magnetic resonance spectroscopic imaging (¹H-MRSI) sequences can address these issues by assessing the entire prostate—providing guidance for targeted biopsies. For example, Puech *et al.*¹ examined 95 men with suspected prostate cancer on the basis of a suspicious lesion detected on mpMRI. MRI-targeted biopsies in these men yielded higher rates of cancer, including clinically significant prostate cancer defined by any Gleason 4 pattern, than a standard systematic 12-core ultrasonography-guided biopsy, particularly in the anterior region of the gland.¹ Although validation is required in a broader unenriched patient population, as is long-term follow up data to accurately determine false-negative biopsy rate, the use of pre-biopsy mpMRI might eventually be incorporated into standard diagnostic algorithms to increase the sensitivity of this approach to detect clinically significant high-grade prostate cancer.

For patients with an established prostate cancer diagnosis, avoiding over treatment of low-risk, clinically insignificant localized prostate cancer has spurred the development of active surveillance strategies that incorporate serial biopsies and PSA measurement. However, despite gains in popularity, concerns regarding the risk of undetected high-grade disease often prompt patients to opt for definitive treatment in the absence of objective evidence of disease up staging. Novel genomic predictive biomarkers can improve upon stand and clinical risk stratification criteria, but are still prone to sampling error related to the biopsy procedure.² Given this limitation, mpMRI might have clinical utility in expanding the number of patients with confirmed low-risk disease who would be appropriate candidates for active surveillance. At the same time, the technique can enhance the ability to detect occult high-grade disease and identify patients who should receive definitive local therapy. One review published in 2013 included 133 patients who underwent mpMRI a median of 60 days before radical prostatectomy.³ The researchers showed that mpMRI was better than common clinical scoring systems (D'Amico, Epstein and UCSF-CAPRA) at correctly classifying patients as appropriate for treatment versus active surveillance on the basis of dominant tumour volume, predominant Gleason pattern and extra capsular or seminal vesicle invasion. Only one of the 13 patients with high-risk pathological disease was classified as low risk on mpMRI. Although prospective validation is required using a standardized MRI scoring system, and integration of recently validated genomic-based prediction scores is essential, mpMRI has the potential to play a key part in improving the accuracy of selecting appropriate candidates for active surveillance.

A new molecular imaging MRI technique, hyperpolarized ¹³C-MRI, which relies on the detection of carbon nuclei rather than protons, also has the potential to improve cancer diagnosis, risk stratification and, in particular, the monitoring of treatment response. ¹³C-MRI provides enhanced spatial and temporal resolution compared with ¹H-MRSI and can be used in the noninvasive real-time assessment of metabolic activity to image cancer. For example, ¹³C-pyruvate—a metabolite involved in the synthesis of lactate via aerobic glycolysis, a pathway upregulated in cancerous cells by way of the Warburg effect—can be used across a spectrum of malignancies that includes prostate cancer. In the first ever phase I study of metabolic MRI using ¹³C-pyruvate reported in 2013, 31 treatment-naïve patients with biopsy-proven localized prostate cancer were enrolled, the majority of whom had Gleason 3 + 3 disease.⁴ Patients were injected with the ¹³C-labelled pyruvate, shortly after which its conversion to lactate could be observed in prostate tumours and, in some cases, in regions of cancer that were not detected by conventional MRI. Although targeted biopsies were not mandatory in the study design, one patient with previously diagnosed Gleason 3 + 3 prostate adenocarcinoma with unilateral disease on MRI was shown to have bilateral elevations in the ratio of lactate to pyruvate on ¹³C-MRI. This patient's tumour was subsequently upstaged and upgraded, to bilateral Gleason 3 + 4 cancer, on directed ¹³C-MRI-guided biopsy. ¹³C-MRI of hyper-polarized pyruvate might, therefore, have a role in detecting occult high-grade disease to aid in treatment selection and prognostication of patients with localized prostate cancer. Future patient studies are needed to define the utility of this imaging modality in assessing treatment response, and prospective studies will be needed to correlate imaging findings with histological grade at the time of radical prostatectomy.

Approximately 25–35% of patients who initially respond to definitive local therapy will experience biochemical relapse. PSA doubling time, Gleason grade at time of diagnosis and time interval from definitive therapy to incidence of relapse are used to predict patterns of recurrence (local regional versus distant), but there is considerable overlap between these clinical metrics. PET-based imaging might offer a more sensitive method of detecting regional disease, distant spread of disease or both than conventional cross-sectional imaging and clinical parameters. A 2013 systematic review and meta-analysis of 19 independent studies highlighted the potential benefit of ^{11}C -choline PET imaging, demonstrating a favourable sensitivity and specificity for detecting recurrent cancer: sensitivity and specificity for detection in the prostatic fossa were 75.4% and 82% and for lymph node metastases were 100% and 81.8%, respectively.⁵ ^{11}C -choline PET was recently approved at the high-volume Mayo Clinic (Rochester, MN, USA) for the detection of recurrent disease. Additionally, ^{18}F -NaF PET has demonstrated increased sensitivity for detecting distant osseous metastases compared with conventional ^{99}Tc bone scanning, including patients with biochemically relapsed disease who are at elevated risk of metastatic disease owing to a rapid rise in serum PSA level.⁶

Androgen deprivation therapy is the standard of care for patients with recurrent or metastatic disease, but all patients eventually develop castration-resistant prostate cancer (CRPC). Considerable molecular heterogeneity underlies the biology of CRPC, with continued reliance on androgen receptor (AR)-mediated signalling that frequently gives rise to AR-independent, c-MYC-driven neuroendocrine prostate cancer (NEPC) as a treatment-emergent adaptive response.⁷ Although no currently available biomarkers are able to readily identify and predict subsets of patients who are most likely to respond to continued AR-directed therapy, new PET-based molecular imaging approaches might offer a suitable alternative and have the potential to accurately distinguish AR-dependent prostate cancer from treatment-emergent NEPC. Indeed, ^{18}F -fluoro-5 α -dihydrotestosterone (^{18}F -FDHT)-PET was used as a pharmacodynamic biomarker of AR ligand binding in the early phase clinical trials of the second-generation AR antagonists ARN-509 and enzalutamide, and helped guide the recommended phase II dose selection of these two agents.⁸ Emerging molecular probes aim to extend the capability of PET imaging to measure downstream AR transcriptional activity. In 2013, one such probe was reported; ^{89}Zr -J591/PSMA, a radiolabelled prostate membrane specific antigen (PSMA) probe, was shown to be inversely related to AR transcriptional activity.⁹ In another example, detection of treatment-emergent NEPC driven by c-MYC was enhanced with the use of ^{89}Zr -transferrin, which binds to the transferrin receptor—a direct transcriptional target of c-MYC. Preclinical studies have demonstrated the feasibility of this approach, and results of the initial clinical studies are eagerly awaited.¹⁰ Finally, the advantages of MRI and PET imaging of prostate cancer are being merged with the development of clinical PET–MRI instruments, which will facilitate a more-comprehensive metabolic and functional characterization of both localized and metastatic disease.⁸

In 2013, key advances in the application of imaging were reported across the spectrum of clinical disease states in prostate cancer. Looking forward, prospectively validating imaging technologies, ideally with concurrent integration of emerging genomic and molecular

analyses, will help to further define the role of imaging in the clinical care of men with prostate cancer.

References

1. Puech P, et al. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy—prospective multicenter study. *Radiology*. 2013; 268:461–469. [PubMed: 23579051]
2. Cooperberg MR, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J. Clin. Oncol.* 2013; 31:1428–1434. [PubMed: 23460710]
3. Turkbey B, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology*. 2013; 268:144–152. [PubMed: 23468576]
4. Nelson SJ, et al. Metabolic imaging of patients with prostate cancer using hyperpolarized [$1\text{-}^{13}\text{C}$]pyruvate. *Sci. Transl. Med.* 2013; 5:198ra108.
5. Evangelista L, et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. *Clin. Nucl. Med.* 2013; 38:305–314. [PubMed: 23486334]
6. Beheshti M, Langsteger W, Fogelman I. Prostate cancer: role of SPECT and PET in imaging bone metastases. *Semin. Nucl. Med.* 2009; 39:396–407. [PubMed: 19801219]
7. Mosquera JM, et al. Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. *Neoplasia*. 2013; 15:1–10. [PubMed: 23358695]
8. Jadvar H. Molecular imaging of prostate cancer with PET. *J. Nucl. Med.* 2013; 54:1685–1688. [PubMed: 24084704]
9. Osborne, JR., et al. A prospective pilot study of ^{89}Zr -J591/PSMA positron emission tomography (PET) in men with localized prostate cancer undergoing radical prostatectomy.. *J. Urol.* <http://dx.doi.org/10.1016/j.juro.2013.10.041>
10. Walia G, Pienta KJ, Simons JW, Soule HR. The 19th annual Prostate Cancer Foundation scientific retreat. *Cancer Res.* 2013; 73:4988–4991. [PubMed: 23536559]

Key advances

- Multiparametric MRI (mpMRI)-targeted biopsies yielded higher rates of prostate cancer detection, including clinically significant (Gleason 4) disease, than standard 12-core guided biopsy, demonstrating its potential for improved risk stratification¹
- mpMRI performed better than clinical assessment scoring systems in predicting which patients were appropriate active surveillance candidates³
- A phase I trial demonstrated the safety and feasibility of hyperpolarized ¹³C-MRI to provide real-time noninvasive assessment of metabolic activity to aid cancer diagnosis, risk stratification and treatment response monitoring⁴
- Two PET agents—¹¹C choline and ¹⁸F-NaF—have been shown to have improved sensitivity compared with conventional imaging in detecting lymph node involvement⁴ and the presence of bone metastases⁵
- New PET-based molecular imaging approaches have promise as biomarkers in advanced-stage prostate cancer, distinguishing between androgen-receptor-dependent^{8,9} and treatment-emergent neuroendocrine prostate cancer¹⁰