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Prostate Cancer

Prostate Cancer Risk Inflation as a Consequence of Image-targeted Biopsy of the Prostate: A Computer Simulation Study

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Abstract

Background: Prostate biopsy parameters are commonly used to attribute cancer risk. A targeted approach to lesions found on imaging may have an impact on the risk attribution given to a man.
Objective: To evaluate whether, based on computer simulation, targeting of lesions during biopsy results in reclassification of cancer risk when compared with transrectal ultrasound (TRUS) guided biopsy.
Design, setting, and participants: A total of 107 reconstructed three-dimensional models of whole-mount radical prostatectomy specimens were used for computer simulations. Systematic 12-core TRUS biopsy was compared with transperineal targeted biopsies using between one and five cores. All biopsy strategies incorporated operator and needle deflection error. A target was defined as any lesion $\geq$0.2 ml. A false-positive magnetic resonance imaging identification rate of 34% was applied.
Outcome measurements and statistical analysis: Sensitivity was calculated for the detection of all cancer and clinically significant disease. Cases were designated as high risk based on achieving $\geq$6 mm cancer length and/or $\geq$50% positive cores. Statistical significance (p values) was calculated using both a paired Kolmogorov-Smirnov test and the t test.
Results and limitations: When applying a widely used biopsy criteria to designate risk, 12-core TRUS biopsy classified only 24% (20 of 85) of clinically significant cases as high risk, compared with 74% (63 of 85) of cases using 4 targeted cores. The targeted strategy reported a significantly higher proportion of positive cores (44% vs 11%; $p < 0.0001$) and a significantly greater mean maximum cancer core length (7.8 mm vs 4.3 mm; $p < 0.0001$) when compared with 12-core TRUS biopsy. Computer simulations may not reflect the sources of errors encountered in clinical practice. To mitigate this we incorporated all known major sources of error to maximise clinical relevance.
Conclusions: Image-targeted biopsy results in an increase in risk attribution if traditional criteria, based on cancer core length and the proportion of positive cores, are applied. Targeted biopsy strategies will require new risk stratification models that account for the increased likelihood of sampling the tumour.

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1. Introduction

The current diagnostic pathway in prostate cancer relies on the transrectal ultrasound (TRUS) guided prostate biopsy test, applied after a man presents with an elevated serum prostate-specific antigen. The random and systematic errors that occur when this test is conducted blind to the location of a cancer have been widely discussed [1–3].

State-of-the-art imaging such as multiparametric magnetic resonance imaging (mpMRI) [4] or novel ultrasound (US) techniques [5] could overcome these errors by providing information on the location and size of suspicious lesions, thus allowing such lesions to be targeted.

Biopsy data are commonly used to determine cancer risk. A targeted approach to lesions found on imaging may have an impact on the risk attributed to a particular man. Features widely used to indicate high risk include Gleason score $\geq$7, as well as parameters to indicate the extent of cancer such as maximum cancer core length (MCCL), maximum percentage cancer, and the number of positive biopsies [6]. However, if a tumour is exposed to a greater sampling density than the rest of the prostate, it is likely that the proportion of cores that are positive and the MCCL will be greater compared with a TRUS biopsy. In addition, higher Gleason patterns, if truly present, are more likely to be sampled.

The aims of this study were to establish whether, and the extent to which, the phenomenon of risk escalation occurs in men who undergo targeted biopsy, by means of a computer simulation.

2. Materials and methods

From 1999 to 2001, 107 consecutive radical prostatectomy whole-mount specimens that underwent 5-mm step sectioning according to the Stanford protocol were analysed [7]. A single histopathologist contoured all cancer foci by hand on each pathology slide. For each slice, the prostate capsule and tumour contours were scanned and digitised using a flatbed scanner. A three-dimensional (3D) computer model/image reconstruction was produced for each gland using custom-written computer software. The scanned two-dimensional cross sections were first aligned. Image registration and a shape-based interpolation method matched the adjacent gland slices to the chosen midgland reference slice [8–11]. A data-specific correction factor was applied to estimate, and thereafter reverse, the fixation-related tissue shrinkage effect [11]. This correction factor, calculated from measurements obtained before and after formalin fixation, was 1.10 (equivalent to a 33% increase in volume), assumed to be isotropic, and applied to all specimens. The detailed methodology for this 3D reconstruction was previously described [12,13].

A false-positive rate for prostate mpMRI was incorporated. This was based on a study recently published [14], in which image-targeted biopsies were performed in 182 men with a lesion suspicious for prostate cancer on mpMRI. MRI false positives are the result of an MRI signal that is incorrect, a targeting miss, or a tissue capture failure. The study demonstrated a 34% mpMRI false-positive rate. Applying this rate to our simulation resulted in a total of 141 prostates for biopsy.

A false-negative rate for prostate mpMRI was not incorporated because men with no lesion on mpMRI have no target for biopsy and therefore revert to the standard of care, the TRUS biopsy.

It was previously demonstrated that lesions $\geq$0.2 ml in volume on mpMRI can be detected with 77% sensitivity and 91% specificity [15]; therefore, we defined a target as any lesion $\geq$0.2 ml.

2.1. Simulated biopsy

For each prostate model, 500 simulations of each biopsy strategy were performed. The biopsy strategies included a 12-core TRUS biopsy and transperineal targeted biopsies. In practice the number of image-targeted cores taken depends on the clinical context and the operator performing the biopsy. Therefore, each simulated transperineal targeted scheme was repeated five times per prostate model, with the number of targeted cores deployed ranging from one in the first series to five in the fifth.

Errors were incorporated for all simulations to reflect registration (or operator) deficiencies and needle deflection. In clinical practice, the total targeting error equates to the sum of these two errors [16]. All biopsy strategies were performed with a range of applied error, from 1 mm to 10 mm (Fig. 1); however, to ensure the results generated were comparable, we set our total targeting error at 5 mm. This error was calculated using (1) a needle deflection error with standard deviation (SD) of 3 mm in any direction (measured at the midpoint of the effective

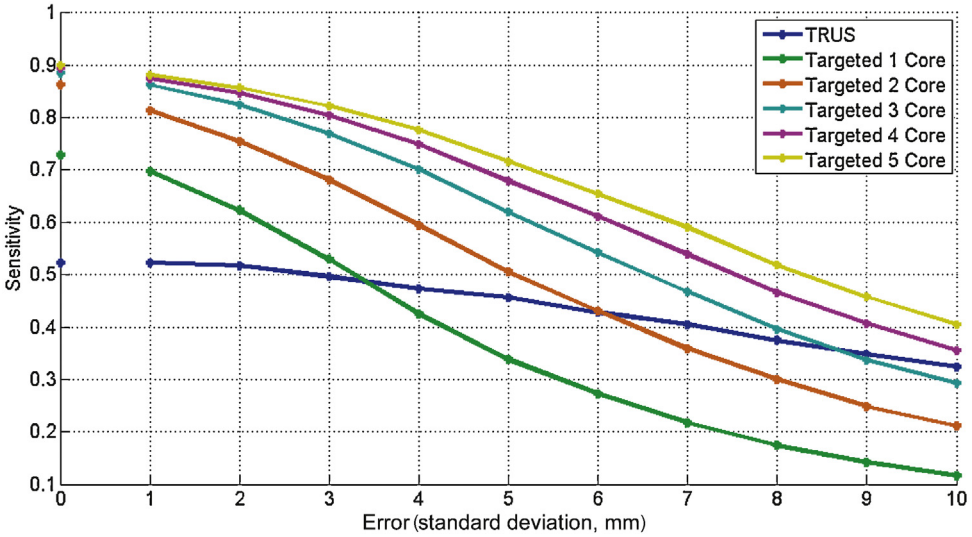

Fig. 1 – All-cancer sensitivity of biopsy simulations with increasing error.