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Original article

Development and internal validation of prediction models for biochemical failure and composite failure after focal salvage high intensity focused ultrasound for local radiorecurrent prostate cancer: Presentation of risk scores for individual patient prognoses

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Abstract

Purpose: Patient selection for focal salvage remains difficult. Therefore, we developed and internally validated prediction models for biochemical failure (BF) and a composite endpoint (CE) following focal salvage high intensity focused ultrasound (HIFU) for radiorecurrent prostate cancer.

Materials and methods: A prospective HIFU registry identified 150 cases (November 2006–August 2015). Recurrence was assessed with multiparametric magnetic resonance imaging (MRI) combined with template prostate mapping biopsies, targeted biopsies, or systematic transrectal ultrasound-guided biopsies. Metastatic disease was ruled out with a positron emission tomography-computed tomography and a bone scan. Focal salvage HIFU consisted of quadrant-ablation, hemi-ablation, or index-lesion ablation. Cox-regression was used for BF (Phoenix-definition) and CE (BF/MRI+/biopsies+/local or systemic treatment/metastases+/prostate cancer specific mortality+). Internal validation was performed using bootstrap resampling (500 datasets) after which C-statistic and hazard ratios were adjusted. Models were calibrated and risk scores created.

Results: Median follow-up was 35 months (interquartile range: 22–52). Median biochemical disease-free survival (DFS) was 33 months (95% CI: 23–45). Median CE-free survival was 24 months (95% CI: 21–35). After multivariable analysis, DFS interval after primary radiotherapy, presalvage prostate-specific antigen (PSA), PSA-doubling time, prostatic volume, and T-stage (both MRI based) predicted BF. For the CE, PSA-doubling time was not predictive but additionally, primary Gleason score was. The adjusted C-statistics were 0.68 and 0.64 for BF and CE, respectively. Calibration was accurate until 48 months. The risk scores showed 3 groups, with biochemical DFS of 60%, 35%, and 7% and CE-free survival of 40%, 24%, and 0% at 4 years.

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Conclusion: Our model, once externally validated, could allow for better selection of patients for focal salvage HIFU.

Keywords: Focal salvage high intensity focused ultrasound (HIFU); Prostate cancer; Prediction models; Biochemical failure; Composite endpoint

1. Introduction

Radiotherapy is an effective treatment for prostate cancer, especially with increasing dose escalation [1]. However, based on pretreatment risk factors, 10% to 50% of patients experience recurrent disease after 10 years [1]. Recurrence is often prostate-confined and related to the index lesion [2,3]. Although most men with radiorecurrent disease receive androgen deprivation therapy (ADT), many might be suitable for local salvage treatment. Whole-gland salvage therapies, such as radical prostatectomy, can confer significant side-effects [4]. Focal salvage therapy where individual areas of recurrent disease are targeted, preserving normal prostatic tissue, might confer fewer side-effects and offer oncological control. Several (pilot) studies using cryosurgery, high intensity focused ultrasound (HIFU) and brachytherapy (BT) have indicated seemingly comparable biochemical control rates, while showing favorable toxicity [5,6].

However, optimal patient selection is unknown. We often use factors associated with biochemical failure (BF) in the primary setting or with whole-gland salvage techniques, since these studies are of adequate size to allow multivariable modeling [4,7–11]. However, the identified risk factors differ in their predictive ability across studies with current prediction models being available only for cryotherapy and I-125 BT [10–12]. Furthermore, established risk factors such as PSA, T-stage, and Gleason score might have different predictive profiles in patients undergoing focal salvage (FS). To date, FS series have been too small and with too short a follow-up to allow adequate modeling of factors to use in patient selection.

Our FS-HIFU dataset has recently reported on overall toxicity and disease control rates in 150 men [6]. We believe this series enables us to create multivariable prediction models to assess the predictive value of a range of risk factors in patients contemplating FS treatment.

2. Materials and methods

2.1. FS-HIFU patients

Exemption from institutional review board was obtained from the UCLH Joint Research Office. Independent prospective academic HIFU registry analysis at 2 centers (University College London Hospitals and NHS Basingstoke Trust) identified 150 men who underwent FS-HIFU between November 2006 and August 2015 for histologically confirmed localized radiorecurrent disease. Selection, diagnostic assessment and treatment details have been described in detail earlier [6,13].

To summarize, all patients were primarily treated with external beam radiotherapy (EBRT) or a combination of EBRT with a high-dose rate (HDR-BT) boost. Patients experiencing BF according to the Phoenix-definition (PSA-nadir + 2 ng/ml) after primary therapy were assessed with multiparametric (mp-)1.5 T-MRI consisting of a T2-weighted, dynamic contrast enhanced and diffusion weighted imaging sequences compliant with international guidelines and the previously published PROMIS study [14]. No endorectal coil was used. Metastatic disease was ruled out using ^{18}F-FDG or choline positron emission tomography-computed tomograph (PET-CT) as well as radio-isotope bone-scan. Patients with radiological stage ≤T3bN0M0 were eligible for FS-HIFU provided T3b patients had minimal (≤1 cm) seminal vesicle invasion. Histological confirmation was obtained using either transperineal 5 mm template prostate mapping biopsies (TPM), multiparametric magnetic resonance imaging (mpMRI) cognitively targeted biopsies or transrectal ultrasound (TRUS)-guided biopsies with treatment offered if histology was concordant with the mpMRI. Other factors such as age, total PSA, PSA-kinetics, and biopsy outcomes were not standardised for selection. Our tertiary center had a policy of offering salvage therapy to men technically suitable for FS-HIFU provided their imaging was negative for metastatic disease. For the purposes of our current modeling, this improves the external validity of our findings.

2.2. Treatment details and follow-up

In case of TRUS-guided biopsies, hemi-ablation was applied if the biopsies and MRI were concordant. Patients with TPM and mpMRI agreement were treated with a focal approach or quadrant-ablation. Index lesion ablation was applied only if the patient had a MRI visible lesion with a concordant transperineal biopsy. It was permissible to leave behind biopsy positive clinically insignificant cancer (≤1 core with ≤3 mm Gleason 3 + 3 or lower) in the contralateral lobe. T3b patients had (part of) the involved seminal vesicle additionally targeted. Follow-up consisted of PSA and toxicity assessment every 3 months. Additional mpMRI and biopsies were performed in cases of rising PSA, clinical suspicion of recurrence or, for biopsies, a suspicious lesion on mpMRI. For residual/recurrent disease, if suitable, a second FS-HIFU procedure was allowed and not deemed failure.

2.3. Variables assessed before primary therapy

Before primary therapy initial PSA value, T-stage, Gleason grade, D'Amico stage, and ADT use were assessed.