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Focal therapy eligibility determined by MRI/US fusion biopsy

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Abstract

Purpose—To assess focal therapy (FT) eligibility among men receiving multiparametric magnetic resonance imaging (mpMRI) and targeted biopsy, with correlation to whole mount histology after radical prostatectomy (RP).

Materials and Methods—Subjects were selected from among the 454 men (2010–2016) with targeted biopsy-proven prostate cancer (CaP) derived from regions of interest (ROI) on mpMRI. FT eligibility was limited to a maximum Gleason score (GS) of 4+3 within ROIs with or without other foci of low-risk CaP (GS 3+3, < 4 mm). Men who did not meet NCCN intermediate risk criteria were classified as ineligible for FT. 64 of the 454 men received RP, and biopsy findings were compared to final pathology.

Results—38.5% (175/454) of men with a biopsy-proven ROI were eligible for FT. Fusion biopsy, which combined both targeted and template biopsy, had a sensitivity, specificity, and accuracy of 80.0% (12/15), 73.5% (36/49), and 75.0% (48/64) respectively for FT eligibility. Targeted cores alone yielded a sensitivity of 73.3% (11/15), a specificity of 47.9% (23/48), and an accuracy of 54.7% (35/64). Discordant cases between biopsy and whole mount histologies differed in GS (4/13) and extension across the midline (9/13).

Conclusions—Using intermediate-risk eligibility criteria, more than one-third of men with a targeted biopsy-proven lesion identified on mpMRI would have been eligible for FT. Eligibility determined by fusion biopsy was concordant with whole mount histology in 75% of cases. Improved selection criteria are needed to reliably determine FT eligibility.

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Keywords

prostate cancer; focal therapy; mpMRI; screening; image-guided biopsy

Introduction

Focal therapy (FT) has the potential to improve management of prostate cancer (CaP), by reducing side effects associated with radical treatment. While the safety and feasibility of FT strategies have been reported using cryoablation,[1] focal laser ablation (FLA),[2] and high-intensity focused ultrasound (HIFU),[3] long-term oncologic efficacy is unknown. A critical barrier to robust testing of FT strategies is appropriate patient selection criteria, which are not clearly established.[4,5] A recent FDA-AUA-SUO workshop on partial gland ablation highlighted this challenge, noting that "some [authors] regard [partial gland ablation] as an alternative to AS for low-risk cancers, whereas others view it as an alternative to radical therapy for selected, higher risk cancers."[6] Regardless of approach, there is broad agreement on the importance of assessment for FT using multi-parametric MRI (mpMRI) followed by targeted biopsy.[6]

To clarify the impact of different patient selection criteria on FT eligibility, we retrospectively studied men who have received MRI/Ultrasound (MRI/US) fusion biopsy, incorporating both targeted and template biopsies. To confirm biopsy findings and to derive the accuracy of fusion biopsy in FT eligibility, we examined whole-organ concordance of eligibility assessment in a subset of patients who underwent radical prostatectomy.[7]

Methods

STUDY COHORT

All men undergoing MRI/US fusion biopsy at UCLA between January 2010 and January 2016 were retrospectively screened for a suspicious lesion identified on mpMRI (UCLA or PI-RADS v2 score 3–5 region of interest, ROI), which was found to contain CaP upon targeted biopsy (Figure 1). FT eligibility criteria, based on the NCCN intermediate-risk definition[8] and recent consensus guidelines,[6] were applied (Table 1). Figure 2 shows histological profiles for FT eligible patients based on biopsy. Three different patterns of CaP are shown, each suitable for treatment by hemi-gland ablation or less. Men with biopsy-negative ROIs were considered ineligible for FT. Similarly, men without csCaP (Gleason score 3+3, maximum cancer core length (MCCL) < 4mm) were also considered ineligible[9], regardless of the number of positive cores. All collection of clinical data was performed prospectively within a UCLA IRB-approved registry.

MRI/ULTRASOUND-GUIDED TARGETED BIOPSY

The fusion biopsy method, which has been previously described, was unchanged throughout the study period.[10,11] Briefly, within 2 months of biopsy, patients underwent a 3T mpMRI with body coil. MRI interpretation was conducted under the direction of a dedicated uro-radiologist (DJM), and suspicious lesions were assessed according to UCLA and Prostate Imaging-Reporting and Data System (PI-RADS) criteria.[10,12] MRI assessment was based on

the UCLA assessment system,[10] which pre-dates PI-RADS v1, and after PI-RADS v2 was established, by both systems using highest suspicion category found. At biopsy, images were registered and fused with real-time transrectal ultrasound (Noblus, Hitachi Aloka, Wallingford, CT) to generate a 3D image of the prostate with delineated ROIs.

Targeted and template cores were taken by a single urologist (LSM) at UCLA Clark Urology Center under local anesthesia using a MR/US fusion and biopsy tracking device (Artemis, Eigen; Grass Valley, CA).[11] A dedicated uro-pathologist interpreted all biopsy cores (JH).

ASSESSMENT OF FOCAL THERAPY STRATEGIES

FT eligibility was assessed using three different ablative strategies (site-specific, quadrant, and hemi-gland) to determine the extent of ablation that would be needed to eliminate the index lesion. The strategies were based on location of cancer-containing biopsy cores in relation to the ROI. Individual biopsy cores from each subject were assessed using database software (PostgreSQL 9.0) to determine eligibility for each strategy. Men with positive biopsy cores limited to the ROI were considered eligible for all FT strategies (site-specific, quadrant, hemi-ablation). Men with positive cores adjacent to the ROI were considered eligible for quadrant and hemi-ablation. Those with ipsilateral but distant positive cores (i.e. in a different quadrant) were considered eligible for hemi-ablation. A visual representation of different strategies can be seen in Figure 3. We evaluated eligibility using both a GS ≤ 4+3 and GS ≤ 3+4 threshold (Table 2).

WHOLE MOUNT PROCESSING OF RADICAL PROSTATECTOMY SPECIMENS

Of the 454 men with biopsy positive ROI, 64 underwent radical prostatectomy (RP) and whole mount processing to facilitate MRI-histological correlation as previously described.[7] Three-dimensional (3D) printed molds were used in cases processed after 2014. Lesion contours identified on whole mount histology were loaded onto custom software and elastically warped to match the mpMRI-defined prostate contour, allowing targets on mpMRI to be directly compared to lesions identified on whole mount histology. Eligibility for FT was then re-assessed based on evaluation of whole mount sections by a dedicated urologic pathologist (JH).

STATISTICAL ANALYSIS

Descriptive statistics for patient characteristics were calculated for each group. Confidence intervals (C.I.) were calculated using a binomial assumption at a 95% threshold. Kruskal-Wallis non-parameteric one-way analysis of variance and post-hoc tests were conducted to measure differences between continuous variables. Pearson chi-squared tests were performed on categorical variables. Statistical significance was considered at $p < 0.05$ for all analyses. Statistical analyses were performed by a coauthor (FJD) using Stata® software, version 13.1. Additional analyses were performed using JMP Pro, version 13.

Results

1408 men in our cohort underwent MRI/US fusion biopsy from 2010–2016. 454 men (32.2%) met the screening criteria in Figure 1. Of the 454 men with at least one biopsy-

positive ROI, 175 (38.5%, 95% C.I. 34.2–43.1%) FT candidates were identified. Of the 914 men with a MRI suspicion score or higher, 19% were FT candidates (95% CI 16.7–21.8%). 57 men with small-volume GS 3+3 cancers were found (12.5%, 95% C.I. 9.8–15.9%). Eight men who would have otherwise qualified for FT were excluded on the basis of PSA > 20 ng/mL. Baseline patient characteristics for FT eligible and ineligible patients are shown in a supplementary table (http://jurology.com). Men were considered ineligible if the ROI contained either insignificant CaP or high-risk CaP. Eligible and ineligible men differed in age, ethnicity, free PSA and PSA density, mpMRI suspicion score, average number of positive cores, incidence of bilateral CaP, MCCL, and GS (all p-values < 0.05, Supplementary Table). While differences between components of inclusion criteria are expected, post-hoc tests nonetheless showed an increasing trend across all three categories (low-risk ineligible, eligible, high-risk ineligible) with total PSA, PSA density, number of positive cores, and maximum cancer core length.

Of the patients with GS ≤ 3+4, 154 (33.9%) were eligible for hemi-ablation or less, 140 (30.8%) for quadrant ablation or less, and 94 (20.7%) for site-specific ablation. When the inclusion criteria included those with maximum GS 4+3, 175 (38.5%) were eligible for hemi-ablation or less, 157 (34.6%) for quadrant ablation or less and 105 (23.1%) for site-specific ablation (Table 2). No man within this study is known to have undergone focal therapy.

ACCURACY OF FT ELIGIBILITY ASSESSMENT

64 men in this series underwent RP as first-line therapy with whole-mount processing of the specimen; 35/64 (54.7%) with 3D-printed molds. Average time from biopsy to surgery was 89.1 ± 32.5 days. Examples of whole mount histology and 3D digital reconstruction are demonstrated in Figure 3. 25/64 patients who underwent RP would have qualified for FT on the basis of biopsy findings. 15/64 men qualified for FT on the basis of whole mount histological findings, with 16 discordant findings (Table 3). Of the 13 patients who were classified as eligible for FT based on fusion biopsy and did not qualify based on whole mount (false positives), 4 were discordant due to a higher GS on whole mount, and 9 were due to the lesion crossing the midline. When examining factors associated with eligibility determined after RP, no significant difference was found for PSA density (p=0.31), prostate volume (p=0.32), or total serum PSA (p=0.09), although the study was not powered for analysis on whole-mount prostatectomy cases.

Targeted and template biopsy, when combined, had a sensitivity, specificity, and accuracy of 80.0%, 73.5%, and 75.0%, respectively for determining eligibility for FT when compared to the whole mount gold standard. Targeted cores alone yielded a sensitivity of 73.3% (11/15), and a specificity of 47.9% (23/48), with an accuracy of 54.7% (35/64).

Discussion

FT has recently emerged as a potentially definitive treatment for localized CaP that aims to preserve quality of life.[13] FT appears promising in initial studies using HIFU, cryotherapy, and FLA,[14] but long-term oncological control has not been established. One key barrier is knowing *a priori* which patients will benefit from partial treatment,[6] with some arguing for

FT as an alternative to surgical intervention, and others for FT as a complement to active surveillance.[15]

While the multifocality of CaP favors whole gland treatment, studies have emphasized the importance of the index lesion as a driver of metastatic potential.[16,17] Recent studies indicate that low grade, low volume lesions behave in an indolent fashion, with limited metastatic potential.[18,19] Contrasting these is a case report by Haffner and colleagues which investigated the clonal origin of lethal prostate cancer and found that its origin arose from a small, low-grade cancer focus in the primary tumor[20]. Nevertheless, more recent and larger studies continue to support the concept that CaP is driven by a single clone,[21] and can be serially tracked with biomarkers and targeted biopsy.[22] Furthermore, FT has been used successfully in treatment of other multifocal solid organ malignancies where secondary lesions have proven to be indolent.[23]

In the present study we estimated the proportion of men diagnosed by MRI/US fusion biopsy who would be eligible for FT. Eligibility criteria from a recent FDA-AUA-SUO workshop on partial gland ablation were used.[6] Biopsy findings were also compared to whole mount histology in a subset of cases. We found that over a third (38.5%) of men with a MRI target and fusion biopsy-confirmed cancer were suitable candidates for FT; nearly a quarter (23.1%) met criteria for site-specific ablation.

Fusion biopsy findings were generally concordant (75%) with whole mount findings, in agreement with findings shown previously.[24] The majority of the false positives (9/13) was attributed to the lesion crossing the midline. In this study, we called lesions that crossed the midline by even a few millimeters as ineligible for any method of focal therapy. In practice, many of these lesions are treatable using a site-specific ablation or ‘hockeystick’ ablation as described by Ahmed et al[25]. Only in a minority (4/25) of cases was assessment through targeted biopsy a failure due to upgrading. While eligibility criteria included GS ≤ 4+3 lesions, 89% of patients met more stringent criteria limited to GS ≤ 3+4. The increased sensitivity of MRI-targeted biopsy for detection of csCaP, widely reported for other situations,[24,26,27] also appears valuable when evaluating for FT eligibility. In our work, over half of eligible men had csCaP localized to within a single ROI, while 40% of men had csCaP outside the index lesion.

Both targeted and template biopsies were important in accurately classifying patients for FT. Overall accuracy using both methods was improved by 20% over using targeted biopsy alone (54% vs. 75%). This suggests that the combined targeted and template biopsy approach is effective at ruling out focal therapy. While whole mount histology of RP specimens are generally concordant with targeted biopsy findings,[24] the moderate agreement in eligibility assessment indicates that improved criteria need to be established. In the univariate analysis of eligible and ineligible patients, PSA density was significantly different between all three cohorts. While the RP data did not show a similar significant difference in PSA density, the difference (p=0.08) suggests that PSA density merits further investigation as a eligibility criterion in a larger, powered study.

While one potential source of error is the registration accuracy between MRI and US (~3 mm),[11,28] a larger issue is the underestimation of true tumor burden by MRI. 52 (29.7%) of eligible patients had csCaP ipsilateral and adjacent to the ROI, qualifying for quadrant ablation. Le Nobin *et al* found that tumors required a 1 cm margin to achieve complete treatment, while Priester *et al* found that the average uniform margin to achieve complete treatment exceeded 1.5 cm.[7,29] This supports the notion that biopsy cores should be taken from beyond the margins of the ROI when evaluating for site-specific or quadrant-based FT. Moreover, these data suggest customization of focal therapy based on data from individual biopsy site locations around the apparent tumor margin.[30] This also suggests that perhaps improved criteria for FT would include individual consideration of the position and size of the lesion, i.e. patient-specific planning, rather than uniform classification.

Several limitations exist that preclude a more general interpretation of the findings presented. This study was hypothesis-generating and retrospective in nature, and was conducted at a single site with all biopsies performed by a single physician. Limited data were available for comparing fusion biopsy findings with whole mount histology. Nevertheless, the significant concordance between the two approaches for determining FT candidacy suggests that fusion biopsy may serve as an important aid to determine eligibility. Further, these results might be used to develop a framework for future prospective studies.

The present findings suggest that (1) more than one-third of patients with a biopsy-proven target (MRI suspicion score ≥ 3) were eligible for FT using consensus criteria; (2) fusion biopsy with both targeting and template samples accurately characterizes the grade and extent of CaP for the purposes of determining FT eligibility.

Conclusion

More than one-third of men with prostate cancer in a MRI-defined region of interest were found to be eligible for focal therapy, using intermediate risk criteria to determine eligibility. MRI/US fusion biopsy, employing both targeting and template biopsies, provided concordance with whole mount histology in determining focal therapy eligibility. Improved criteria are needed in order to determine FT eligibility with accuracy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

3D	Three Dimensional

CaP	Cancer of the prostate
FLA	Focal laser ablation
FT	Focal Therapy
GS	Gleason Score
HIFU	High Intensity Focused Ultrasound
MCCL	Maximum Cancer Core Length
mpMRI	Multiparametric Magnetic Resonance Imaging
MRI/US	Magnetic Resonance Imaging /Ultrasound
NCCN	National Comprehensive Cancer Network
PI-RADS	Prostate Imaging – Reporting and Data System
ROI	Region of Interest
RP	Radical Prostatectomy
US	Ultrasound

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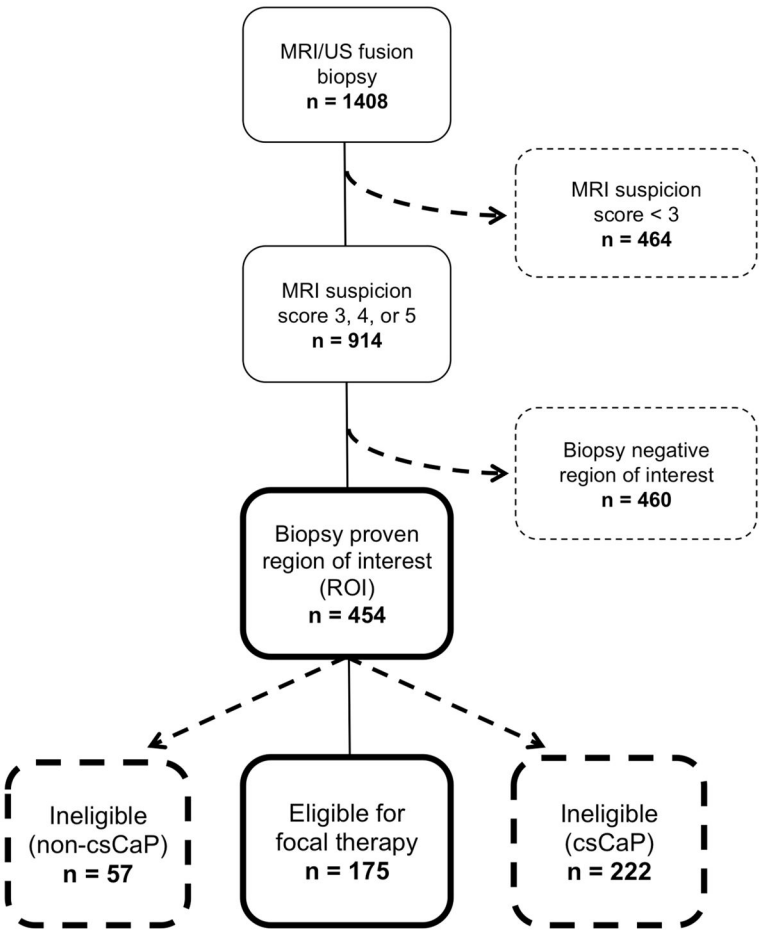

Figure 1.

Flow chart of patient selection for focal therapy eligibility. All patients undergoing MRI/ultrasound fusion biopsy from March 2010–January 2016 were screened for inclusion. Of the 1408 patients screened, 454 were found to have prostate cancer in an MRI-defined region of interest (ROI). Men with csCaP outside of a biopsy-proven ROI were still eligible for focal therapy if it was ipsilateral to the ROI.

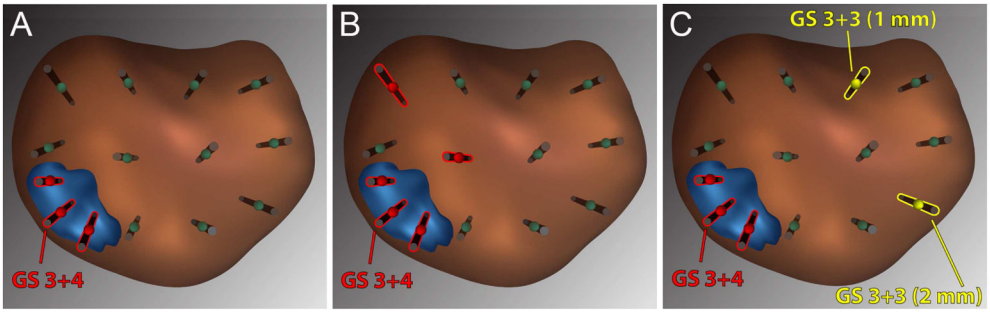

Figure 2.

Examples of 3 different CaP patterns, each eligible for FT, as determined by MRI/US fusion biopsy. Blue = index lesion; red = biopsy positive for csCaP (GS3+4 OR GS3+3, MCCL ≥ 4 mm); yellow = biopsy positive for GS3+3, MCCL < 4 mm (non-csCaP). A. Patient is eligible for site-specific, quarter-gland, or hemi ablation with only positive cores found in target; B. Patient is eligible for hemi-gland ablation with positive cores found on only one side; C. Patient is eligible for any ablation strategy; non-csCaP in the contralateral lobe does not rule out FT. Both systematic (template) and targeted sampling were used to determine eligibility.

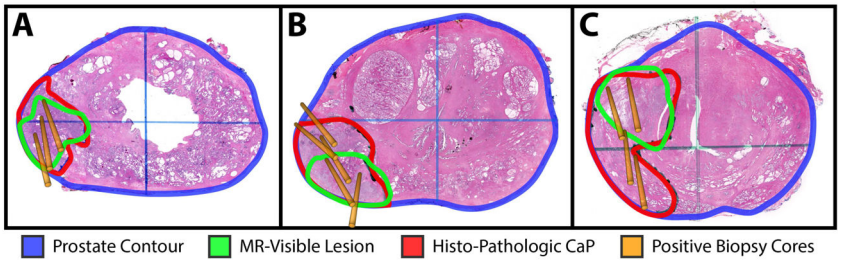

Figure 3.

Focal therapy treatment strategies vs actual pathology seen on whole-mount (WM) sections. *A*, Site-specific ablation – WM histology outlines a single focus of GS 4+3 CaP (red), enclosing the mpMRI-derived target (green). Positive fusion biopsy cores (orange) were found only within the target. *B*, Quarter gland ablation – WM histology outlines a single focus of GS 3+4 CaP (red) limited to one quarter of the prostate. Positive fusion biopsy cores (orange) were found both within the target (green) and adjacent to it. *C*, Hemi-gland ablation – WM histology outlines a large focus of GS 3+4 CaP (red) limited to one lobe of the prostate. Positive biopsy cores (orange) were found both within the target (green) and on adjacent template sites. Reduced from 1x.

Table 1

Focal therapy eligibility criteria, based on the NCCN intermediate-risk definition[9] and recent consensus guidelines[7].

Eligibility criteria:
Clinical stage ≤ T2c
Serum PSA ≤ 20 ng/mL
ROI on mpMRI grade ≥ 3
csCaP within mpMRI-derived ROI, defined as
GS ≤ 4+3 in any core, or
GS 3+3 with maximum cancer core length (MCCL) ≥ 4mm
At least 10 template and 2 targeted cores obtained, demonstrating unilateral csCaP
Ineligible:
Clinical stage ≥ T3a
Serum PSA > 20 ng/mL
GS > 4+3 CaP in any core
Bilateral csCaP (GS 3+3 and MCCL ≥ 4 mm OR any GS ≥ 3+4)
Absence of csCaP

Table 2

Assignment of eligible patients into various FT strategies

	Site-specific ablation n (%)	Quadrant ablation n (%)	Hemi-ablation n (%)
GS ≤ 3+4	94 (20.7)	140 (30.8)	154 (33.9)
95% C.I.	17.2–24.7%	26.8–35.2%	29.7–38.4%
GS ≤ 4+3	105 (23.1)	157 (34.6)	175 (38.5)
95% C.I.	19.5–27.2%	30.4–39.1%	34.1–43.1%

Table 3

Sensitivity and specificity of fusion biopsy (FB) prediction of focal therapy eligibility, compared to findings on whole mount (WM).

	WM Eligible	WM Ineligible	Total
FB Eligible	12	13	25
FB Ineligible	3	36	39
Total	15	49	64
	Sensitivity = 80.0%	Specificity = 73.5%	Accuracy = 75.0%