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ORIGINAL ARTICLE

Combination of multiparametric magnetic resonance imaging and transrectal ultrasound-guided prostate biopsies is not enough for identifying patients eligible for hemiablative focal therapy for prostate cancer

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Abstract

Purpose To evaluate focal therapy (hemiablation) eligibility in men undergoing prostate biopsy and multiparametric magnetic resonance imaging (mpMRI) with reference to histopathology from radical prostatectomy (RP) specimens.

Methods Subjects were selected among 810 men who underwent prostate biopsy, mpMRI, and RP from January 2016 to December 2017. Hemiablation eligibility criteria were biopsy-proven unilateral cancer, prostate-specific antigen ≤ 15 ng/ml, and Gleason score (GS) ≤ 3 + 4. Evidence of non-organ-confined disease or Prostate Imaging Reporting and Data System score ≥ 4 on the contralateral lobe on mpMRI was classified as ineligible for hemiablation. Of the 810, data for 185 who met the screening criteria were compared to final pathology findings. Significant cancer at RP was defined as any of the following: (1) GS 6 with tumor volume ≥ 0.5 ml; (2) GS ≥ 3 + 4; or (3) the presence of advanced stage (≥ pT3).

Results Among the 185 candidates for hemiablation, 62 (33.5%) had unilateral cancer on final RP histopathology. Among the 123 bilateral cancers, 50 (27%) were organ confined and had GS ≤ 3 + 4 = 7 and bilateral multifocal tumor in which the index tumor was confined to one lobe and the secondary tumor in the contralateral lobe had tumor volume < 0.5 ml and GS ≤ 6. A total of 112 (60.5%) patients in this series were considered suitable for hemiablation. Significant cancer on biopsy and mpMRI-negative lobes were found in 72 (38.9%) of 185 lobes, including 1 (0.5%) with advanced stage.

Conclusions The combination of standard prostate biopsy and mpMRI did not accurately identify lobes that could be considered as non-treated regions.

Keywords Focal therapy · Hemiablation · Magnetic resonance imaging · Prostate biopsy · Prostate cancer

Introduction

Focal therapy (FT) is defined as selective ablation of specific areas of the prostate with preservation of the remaining area [1]. FT has emerged in recent decades as a treatment option for men with localized low-to-intermediate-risk prostate cancer that minimizes treatment-related morbidities, particularly incontinence and impotence. The modalities used for FT are various, and FT may reduce complications associated with whole gland therapy provided that similar oncologic outcomes are maintained [1, 2].

Multiparametric magnetic resonance imaging (mpMRI) is an important imaging tool for characterizing and targeting prostate cancer in clinical practice and FT. However, addition of systematic biopsies remains essential for accurately staging of disease [3]. mpMRI and prostate biopsy modalities are associated with high negative predictive value (NPV) for significant cancer in non-treated regions considered to be "normal".

Detailed clinical staging is essential for selecting patients suitable for FT. Several consensus protocols recommend

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consideration of FT in patients with low-risk [Gleason score (GS) 3 + 3] tumors and life expectancies of at least 10 years [4–6]. The International Delphi Consensus Project recommends FT for patients with low-/intermediate-risk cancer (D'Amico), including GS 4 + 3. GS 3 + 4 cancer, where localized, foci < 1.5 cc on mpMRI, or < 20% of the prostate is suitable for FT (up to 3 cc or 25% of the prostate for hemiablation). GS 6 is acceptable in one core from the non-treated region [7].

Korean patients have an increased risk of high-grade prostate cancer and higher prostate-specific antigen (PSA) than Americans [8]. Jeong et al. [9] reported that Korean men had an approximately 60% increased risk of advanced stage and approximately 3 times increased risk of high-grade prostate cancer as compared to African Americans after adjusting for age, PSA, prostate volume, and clinical stage. Even in a subgroup of patients with low-risk prostate cancer (PSA < 10 ng/ml, cT1 stage, and biopsy GS 6), both upgrading to GS 4 + 3 or higher and upstaging to pT3 or higher were more common in Korean men than in Western men. In patients with biopsy-proven prostate cancer with GS 6 who underwent radical prostatectomy (RP), the rate of GS upgrading was 54.1% and 74.1% in PI-RADS scores 1–3 and 4–5, respectively [10].

However, there is no information regarding the number of patients suitable for FT based on data from RP specimens. Therefore, in this study we investigated the histopathological features of clinically localized prostate cancer to evaluate the accuracy of combined prostate biopsy and mpMRI for identifying patients suitable for hemi-ablative FT.

Patients and methods

Patients

Institutional Review Board (IRB) of Samsung Medical Center approved this retrospective study and waived the requirement for informed consent (IRB no. 2018-05-091). From January 2016 to December 2017, 913 consecutive men age ≥ 40 years old underwent RP at a single center. Among them, we excluded 34 patients who received hormone therapy before surgery, 33 patients with data missing from the prostate biopsy, 34 patients with no Prostate Imaging Reporting and Data System (PI-RADS) scores on mpMRI, one patient with no malignancy on RP, and one patient with rhabdomyosarcoma on RP. In total, 810 patients had evaluable data and were included.

Data collection

The preoperative clinical features of patients, including age, PSA level, number of biopsy cores and positive cores, GS on biopsies, PI-RADS scores on mpMRI, and clinical tumor stage, were reviewed using electronic medical records. Two blinded, experienced radiologists (10 and 15 years of experience) independently reviewed the different mpMRI images separately for tumor scoring using validated PI-RADS v2. PI-RADS v2 assessment categories were defined as follows score 1 (low) to score 5 (high) according to the likelihood of significant prostate cancer being present [11–13]. Using the RP specimens, we recorded the total tumor number and volume, the highest GS, and the pathological stage. The GS, location, and volume of each tumor focus were also recorded.

Tumor laterality was based on the urethra as a midline in the sagittal plane. "Bilateral unifocal" refers to the presence of one tumor crossing the midline and "bilateral multifocal" refers to the presence of at least one tumor in each of the left and right lobes.

Based on the RP specimens, lobes were stratified into lobes with insignificant cancer, significant cancer, or no cancer. We also compared these data with preoperative biopsy lobe results. Significant prostate cancer at RP was defined as any of the following: (1) GS 6 with tumor volume ≥ 0.5 ml; (2) GS ≥ 3 + 4 = 7; or (3) the presence of extracapsular extension (ECE) or seminal vesicle invasion (SVI). If index tumors extended into the contralateral lobe, both lobes were defined as lobes with significant cancer [14].

Patients underwent open, laparoscopic, or robot-assisted RP. One experienced genitourinary pathologist examined all biopsy and RP specimens according to the International Society of Urological Pathology protocols.

Suitability for focal therapy (hemiblation)

We applied FT eligibility criteria based on the consensus project derived from the Delphi method [6] and from the recent prospective high intensity-focused ultrasound (HIFU) hemiablation trial [15]. Patients who would have been considered suitable for hemiablation were retrospectively selected based on the criteria that include PSA 15 ng/ml or less, biopsy-proven unilateral prostate cancer, and GS of 3 + 4 = 7 or less on systematic transrectal ultrasound (TRUS) 12-core prostate biopsy or mpMRI-guided target biopsy plus systematic biopsy. Patients with evidence of non-organ-confined disease (ECE or SVI) or PI-RADS score of 4 or greater in the contralateral lobe on mpMRI were excluded (Table 1). A total of 185 patients were identified as suitable candidates for hemiablation.

Results

A total of 810 consecutive men underwent prostate biopsy, mpMRI, and RP. Of these patients, 625 were excluded from the analysis, as they did not meet the patient selection

Table 1 Patients excluded from the analysis

Reason for exclusion	Number of patients
PSA > 15 ng/ml	121
Bilateral prostate cancer	286
Gleason score ≥ 4 + 3	125
Evidence of ECE or SVI on mpMRI	20
PI-RADS score on the contralateral lobe on mpMRI ≥ 4	73
Total number of patients excluded from the analysis	625

ECE extracapsular extension, *mpMRI* multiparametric magnetic resonance imaging, *PI-RADS* Prostate Imaging Reporting and Data System, *PSA* prostate specific antigen, *SVI* seminal vesicle invasion

criteria for hemiablation. As a result, 185 (22.8%) met the screening criteria (Fig. 1).

The baseline characteristics of FT eligible patients who were included in the analysis are described in Table 2. On positive prostate biopsy sides, there were 131 (70.8%) regions of interest with PI-RADS scores 4–5 and 81 (43.8%) with GS 3 + 4 = 7. Median (range) time from biopsy to surgery was 50.52 (22–808) days.

Individual tumor characteristics from RP specimens are presented in Table 3. The majority of the cases were bilateral multifocal (53%) and the mean (median) overall tumor volume was 1.63 (10.7) ml.

Of the 810 patients who underwent biopsy, mpMRI, and RP, 185 would have qualified for hemiablation based on biopsy and mpMRI findings and 154 qualified for hemiablation based on RP specimen histological findings. There were 115 discordant findings (Table 4). The false-positive results had 73 patients who were classified as eligible for hemiablation based on biopsy and mpMRI, and who did not qualify based on the RP specimen. Combination prostate biopsy and mpMRI had 72.7% sensitivity (112 of 154 cases), 88.8% specificity (583 of 656), and 85.8% accuracy (695 of 810) for hemiablation eligibility.

The pathological concordance and disagreement between the prostate biopsy and the RP specimen according to the positive and negative biopsy lobes are shown in Table 5. A positive biopsy lobe showed a higher concordance (83.8%) as compared to a negative biopsy lobe (30.3%). Histological findings of RP were underestimated by the biopsy, which led to upgrading and upstaging rates of 9.2% and 11.9%, respectively, for the positive lobes. Significant prostate cancer was found on the negative biopsy lobe in 72 (38.9%) patients, including 1 (0.5%) with non-organ-confined disease. The false-negative rate of any cancer was 69.7% (129 of 185) on the negative biopsy lobe.

Figure 1 illustrates the proportion of patients suitable for hemiablation. Among the 185 candidates for hemiablation, 62 (33.5%) had unilateral cancer on the final RP histopathology. Among the 123 bilateral cancers, 50 (27%) had organ

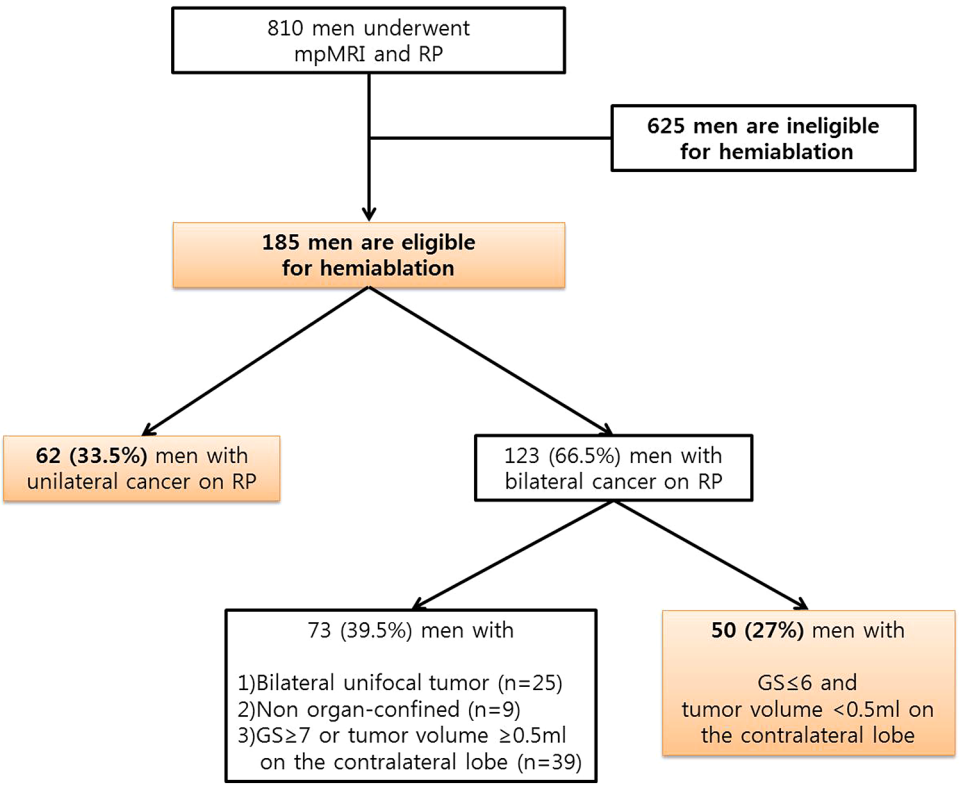

Fig. 1 Patients considered suitable for hemiablation based on biopsy and mpMRI results. *GS* Gleason score, *mpMRI* multiparametric magnetic resonance imaging, *RP* radical prostatectomy

Table 2 Baseline characteristics

Characteristics	Value
Number of patients	185
Mean (median) age, years	64.79 (64.0)
Mean (median) PSA, ng/ml	5.19 (4.59)
Biopsy	
Mean (median) number of biopsy cores	11.3 (12.0)
Mean (median) number of positive cores	2.63 (2.0)
Gleason score 3 + 3 = 6, *n* (%)	104 (56.2)
Gleason score 3 + 4 = 7, *n* (%)	81 (43.8)
mpMRI findings of the negative biopsy lobe	
PI-RADS score 3, *n* (%)	17 (9.2)
PI-RADS score 1–2, *n* (%)	168 (90.8)
Clinical tumor stage, *n* (%)	
T1c	51 (27.6)
T2a or b	134 (72.4)
Days from biopsy to radical prostatectomy, median (range)	50.52 (22–808)
Radical prostatectomy methods, n (%)	
RRP or RPP	22 (11.9)
LRP	4 (2.2)
RALRP	159 (85.9)

LRP laparoscopic radical prostatectomy, *mpMRI* multiparametric magnetic resonance imaging, *PSA* prostate specific antigen, *RALRP* robot-assisted laparoscopic radical prostatectomy, *RPP* radical perineal prostatectomy, *RRP* radical retropubic prostatectomy, *PI-RADS* Prostate Imaging Reporting and Data System

Table 3 Tumor characteristics from 185 radical prostatectomy specimens

Variable	Value
Tumor focality, *n* (%)	
Unifocal	77 (41.6)
Multifocal	108 (58.4)
Tumor laterality, *n* (%)	
Unilateral unifocal	52 (28.1)
Unilateral multifocal	10 (5.4)
Bilateral unifocal	25 (13.5)
Bilateral multifocal	98 (53.0)
Overall tumor volume, ml, mean (median)	1.63 (1.07)

confined, GS ≤ 3 + 4 = 7, and bilateral multifocal tumors in which the index tumor was confined to one lobe and the secondary tumor in the contralateral lobe had a tumor volume < 0.5 ml and GS ≤ 6. Therefore, 112 (60.5%) patients in this series could be considered suitable for hemiablation.

There were 17 patients with PI-RADS score of 3 on the contralateral lobe. Of these, there was no cancer in seven patients, five patients had a GS 6, and five patients had a GS 3 + 4. Therefore, only five patients (GS 3 + 4) could be considered unsuitable for hemiablation. Even in subgroup analysis, when PI-RADS ≥ 3 was applied to the contralateral lobe as an exclusion criteria, 101/168 (60.1%) patients could be considered suitable for hemiablation (Supplementary Fig. 1).

Table 4 Sensitivity and specificity of prostate biopsy and mpMRI prediction of hemiablation eligibility versus radical prostatectomy specimen findings (*n* = 810)

Prostate biopsy and mpMRI[a]	No. of radical prostatectomy specimens		Total no.
	Eligible	Ineligible	
Eligible	112	73	185
Ineligible	42	583	625
Total	154	656	810

mpMRI multiparametric magnetic resonance imaging

[a]Sensitivity 72.7% (112/154), specificity 88.8% (583/656), and accuracy 85.8% (695/810)

Discussion

When compared to established standard treatments, such as RP or radiotherapy that treat the whole gland, FT has the potential to improve prostate cancer treatment by reducing side effects [16]. However, available data regarding FT strategies remain poor and inconclusive and, to our knowledge, long-term oncologic outcomes are unknown [17]. Patient selection is a critical element challenge limiting FT adoption and use [18]. Although several consensus meetings have strived to define patient selection criteria, such criteria have not been clearly established [6, 18].

In the present study, we estimated the proportion of men who would be eligible for hemiablation using prostate biopsy and mpMRI. We implemented eligibility criteria based on consensus regarding FT trial design [6] and a recent phase II trial of FT (hemiablation) [15]. We also compared biopsy findings with histology findings from RP specimens. Of 185 patients deemed eligible for hemiablation by biopsy and mpMRI, 60.5% (112 of 185) were suitable for hemiablation.

To our knowledge, only one study previously evaluated the accuracy of combined mpMRI and transperineal template-guided mapping biopsy (TTMB) of the prostate to identify candidates for hemiablation [14]. Of the 50 patients studied (PSA ≤ 15 ng/ml, T-stage ≤ T2a, GS on biopsy ≤ 3 + 4, no evidence of ECE or SVI on mpMRI), 21 had significant unilateral cancer on mpMRI + TTMB and were potential candidates for hemiablation. Of these 21 patients, 19 (90%) had significant unilateral cancer on the final RP histopathology. Although the sample size of 50

Table 5 Pathological concordance and disagreement between prostate biopsies and RP specimens according to positive versus negative biopsy lobes

	Positive biopsy lobe, *n* (%) Gleason score ≤ 3 + 4 Organ-confined disease	Negative biopsy lobe, *n* (%) No cancer PI-RADS ≤ 3 on mpMRI
Concordance	155 (83.8%)	56 (30.3%)
Disagreement		
Upgrading	17 (9.2%)	129 (69.7%)[a]
Upstaging (non-organ-confined)	22 (11.9%)	1 (0.5%)
Gleason Score		
3 + 3	49 (26.4%)	66 (35.7%)
3 + 4	113 (61.2%)	56 (30.2%)
≥ 4 + 3	17 (9.2%)	7 (3.8%)
Tumor volume ≥ 0.5 ml	118 (63.8%)	55 (29.7%)
Significant prostate cancer	142 (76.7%)	72 (38.9%)

Concordance is defined as (1) positive biopsy lobe: Gleason score ≤ 3 + 4 and organ-confined disease on RP specimen and (2) negative biopsy lobe: no cancer on RP specimen. Upgrading is defined as (1) positive biopsy lobe: Gleason score ≥ 4 + 3 on RP specimen and (2) negative biopsy lobe: any cancer on RP specimen

mpMRI multiparametric magnetic resonance imaging, *PI-RADS* Prostate Imaging Reporting and Data System, *RP* radical prostatectomy

[a]False-negative rate

patients was small, this combination showed high accuracy in predicting FT candidates. Using the TTMB, more accurate patient selection was made possible. Transperineal template-guided saturation biopsy is currently suggested to aid in patient selection [6, 19, 20].

Another previous study assessed FT eligibility by MRI/TRUS fusion biopsy [16]. In this series, 64 men underwent RP, of whom 25 would have qualified for FT based on fusion biopsy findings and 15 for FT based on whole-mount histological findings. This combination yielded 75% accuracy (48 of 64) for FT eligibility, and 48% (12 of 25) were actual potential candidates for FT. In this study, the criteria for FT eligibility were less strict because the PSA was < 20 ng/ml and GS ≤ 4 + 3. The highlight of our study is that we compared biopsy results with RP specimen findings in a larger number of subjects than in the two previous studies.

When considering hemi-ablative FT, detecting high NPV of significant prostate cancer in regions considered to be non-treated lobes is important for selecting patients suitable for hemiablation. Matsouka et al. [21] conducted extended prostate biopsies combined with diffusion-weighted imaging (DWI) to identify prostate lobes without significant cancer. There were a total of 270 sides examined in the study, of which 46 (17.0%) had negative DWI findings and prostate biopsy data. Of the 46 sides, significant cancer was absent in 95.7% (44 of 46) based on pathologic examination of the RP specimens. However, indolent cancer was defined as organ-confined disease with tumor volume < 0.5 ml and GS ≤ 3 + 4 without Gleason pattern 5. Although there is no consensus regarding the identification of indolent cancer, without taking into account the percentage of Gleason 4 cases present, these criteria seem to identify more indolent cancer.

Two prospective studies with hemiablative HIFU for unilateral localized prostate cancer were recently published. Although the study designs were different from that of the present study, similar patient inclusion criteria were used. Ganzer et al. [15] performed a prospective study in patients with clinical stage T1c–T2a, unilateral cancer, GS of 3 + 4 or less, and PSA 10 ng/ml or less. Exclusion criteria were evidence of significant cancer on the contralateral side on mpMRI as defined by a score of 4 or greater on PI-RADS. Unilateral cancer was assessed by TRUS-guided biopsy and mpMRI. Hemiablation was performed using HIFU. Biopsies at 12 months after treatment were positive for clinically significant prostate cancer in 1 (2.0%) of the 49 patients on the untreated side. In another similar study [22], Rischmann et al. found 7 (7.0%) of 101 positive biopsies on the untreated lobe. However, our study showed a 38.9% false-negative rate for significant cancer in negative biopsy and PI-RADS < 4 lobes, which is higher than the rates in other studies. Similar to our study, unilateral prostate cancer was assessed using TRUS biopsy and mpMRI was used to exclude the possibility of significant cancer on the contralateral side. However, the follow-up biopsy results of the previous two studies and our RP specimen pathologic results showed large differences. The first possible reason for this is that a significant proportion of prostate cancers in Korean patients exhibit poor differentiation regardless of the initial PSA level or clinical stage at presentation [23]. Second, the absence of clinically significant cancer on biopsy may be inaccurate

as a surrogate for true significant cancers diagnosed on whole-mount analysis. However, the two previous prospective studies can not actually perform the RP to analyze the results. Therefore, our retrospective analysis also provides important information on patient selection for FT. If hemiablation had actually been performed, it was possible that there would have been under treatment in about a quarter of the patients.

The present study had several limitations. First, this study was retrospectively conducted at a single center, raising concern regarding selection bias. Higher risk patients were included because we analyzed only men who underwent RP. Many patients with low-risk prostate cancer underwent alternative treatment options, such as active surveillance and FT. Thus, many men considered suitable for FT may have been excluded from our analysis. Second, heterogeneity in the prostate biopsies performed in this study resulted from the use of both TRUS-guided biopsy and mpMRI-guided target biopsy. Most targeted biopsies using mpMRI were performed in patients with a previously negative TRUS biopsy with persistently elevated PSA levels. Third, because our study was designed to identify candidates for hemiablative FT, we focused on side-specific analyses. Therefore, analyses based on whole-mount processing were not included, a shortcoming that could be addressed in a future study. A validation study using the same biopsy methods or TTMB would also be valuable for confirming the results of the current study. Lastly, a single genitourinary pathologist reviewed all slides, and interobserver variability for Gleason grading was not evaluated. However, the reviewer had been in practice for more than 20 years.

Conclusion

The success of FT is dependent on appropriate patient selection, which requires an accurate investigative tool that can exclude significant cancer on the contralateral side from the lobe intended to for ablation while precisely localizing the index tumor to be ablated. The combination of standard prostate biopsy and mpMRI did not accurately predict lobes that would be considered as non-treated regions. The future development of mpMRI with PI-RADS evaluation is necessary to help accurately identify men with prostate cancer that is appropriate for focal therapy.

Authors' contributions YH Choi: data analysis, manuscript writing and editing, JW Yu: data collection and analysis, MY Kang: data analysis, HH Sung: data analysis, BC Jeong: data collection and management, SI Seo: data collection and management, SS Jeon: data collection and management, HM Lee: data analysis, HG Jeon: project development, data analysis, and supervision.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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