RARP in high-risk prostate cancer: use of multi-parametric MRI and nerve sparing techniques

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To examine the outcomes of patients with high-risk prostate cancer (PCa) treated by robot-assisted radical prostatectomy (RARP) and evaluate the value of multi-parametric magnetic resonance imaging (MRI) in estimating tumor stage, extracapsular extension, and grade, and the application of nerve sparing (NS) techniques. Patient demographics, preoperative imaging, surgical parameters, pathological features, functional and recurrence outcomes were collected retrospectively in patients with high-risk PCa who underwent RARP between December 2009 and October 2013. Pathological whole mount slides to assess NS were compared with potency, recovery of continence, and surgical margins (SM). Forty-four cases of high-risk PCa were identified with a median followup of 24 months and positive surgical margins (PSM) rate of 14%. Continence returned in 86%, with potency rate of 58%. Of the 25 cases with a preoperative multi-parametric MRI, MRI improved clinical staging from 28% to 88%, respectively. Following risk stratification of NS by microscopic analysis of whole mount pathology, patients with Group A (bilateral NS), Group B (unilateral NS), Group C (partial NS), and Group D (non-NS) had 100%, 92%, 91%, and 50% continence rates, and 100%, 80%, 45%, and 0% potency rates, respectively, with an inverse correlation to PSM. RARP in men with high-risk PCa can achieve favorable oncologic and functional outcomes. Preoperative MRI may localize high-grade tumors and improve clinical staging. Extent of NS is influenced by clinical staging and may balance potency and continence with PSMs.

Keywords: magnetic resonance imaging; nerve sparing; prostate cancer; robot-assisted radical prostatectomy

INTRODUCTION

Robot-assisted radical prostatectomy (RARP) has become a widely adopted procedure to treat localized prostate cancer (PCa). Its use in high-risk patients has gained acceptance by urologists in experienced centers.¹⁻⁴ Recovery of continence and potency, positive surgical margins (PSM), biochemical recurrence (BCR), and use of adjuvant treatments remain surrogates of efficacy in evaluating the validity of the robotic approach.⁵⁻⁶ Recently, multi-parametric magnetic resonance imaging (MRI) has been reported in predicting tumor location, extracapsular extension (ECE), and tumor grade prior to radical prostatectomy.⁷⁻⁻¹⁰

Here, we retrospectively examined our high-risk PCa patients to assess the impact of selected use of multi-parametric MRI as well as whole mount pathology to correlate risk-stratified NS with continence, potency, PSMs, and BCR.

MATERIALS AND METHODS

During the period of months between December 2009 and October 2013, 44 men with high-risk PCa underwent RARP by a single surgeon. High-risk patients according to D’Amico’s risk classification was defined by prostate-specific antigen (PSA) ≥20 ng ml⁻¹, clinical stage ≥T2c, or Gleason grade score ≥8 and The American Joint Committee on Cancer 2002 staging guidelines.¹¹⁻¹² Patient demographics, surgical parameters, pathological staging, functional outcomes, and use of additional therapy were collected. Postoperative PSA was obtained initially at 6 weeks and every 3 months thereafter. PSA recurrence using ultrasensitive PSA was defined as ≥0.05 ng ml⁻¹ with a rising slope.¹³ Continence was defined as use of no pads per 24 h.¹⁴ Postoperative potency was defined as the ability to have successful intercourse (score of ≥4 on question two of the SHIM) with or without the use of PDE5 inhibitors.¹⁵ This study was approved by our Institutional Review Board.

Magnetic resonance imaging protocol

Magnetic resonance imaging of the pelvis was performed on a 3 Tesla scanner (Magnetom Trio, Siemens Healthcare, Erlangen, Germany). Axial whole pelvis T1-weighted and T2-weighted turbo spin echo (TSE) images were obtained. Small field of view sagittal, axial oblique, and coronal oblique T2-weighted TSE high-resolution images and diffusion-weighted images with apparent diffusion coefficient (ADC) map were obtained. Pre- and dynamic post-contrast three-dimensional axial fat saturated gradient recalled echo T1-weighted images were acquired with the intravenous administration of 15 cm³ of Multihance. Time from MRI to surgery was noted. MRI studies were interpreted by either one of two experienced radiologists, with tumor location, mean ADCs, and capsular involvement data collected.

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Nerve sparing grading
Nerve sparing was stratified into four novel risk groups based on a previously described NS criteria following examination of pathologic whole-mount step sections.1 Previously, Grade I NS, the Denonvilliers' fascia and the lateral pelvic fascia (LPF) are incised just lateral to the prostatic capsule to preserve the neural hammock, Grade II NS, the Denonvilliers' fascia and LPF are incised just lateral to the layer of veins on the prostate capsule, Grade III NS, an incision is made through the outer compartment of the LPF, excising all layers of Denonvilliers' fascia, and Grade IV NS, a wide excision was performed of the LPF and Denonvilliers' fascia containing most of the periprostatic neurovascular tissue. We modified this system which originally determined NS grade as the higher (less NS) of the two sides, with the following groups: (a), bilateral NS, Grade I on both sides, (b), unilateral NS, unilateral Grade I and Grade II–IV on the contralateral side, (c), partial NS, unilateral Grade II on one side or III and Grade II, III or IV on the contralateral side, and (d), non-NS, Grade IV on both sides (Figure 1).

Statistical analysis
For descriptive statistics, medians, and interquartile ranges (IQR) were reported as a continuous variable, while the number and percentage were used as categorical variables. Unpaired Student's t-tests were used for continuous variables, while Chi-square tests were used for categorical variables.

RESULTS
Oncological and functional outcomes
The patient demographics include median age at surgery of 64 years, age-adjusted Charlson score of five, and body mass index of 28 kg m⁻² (Table 1). Median estimated blood loss was 100 ml, transfusion rate of 0%, and a median hospital stay of 2 days. Complications included four (9%) Clavien one complications, and two (5%) Clavien Grade 3 complications, one consisting of a urine leak requiring percutaneous drainage (2%), and the second gross hematuria requiring clot evacuation under anesthesia (2%). The rate of PSM was 14% and lymph node positivity was 7%. Androgen deprivation therapy (ADT) was performed in two (5%) cases, including one patient receiving immediate adjuvant ADT following node positive disease with postprostatectomy nadir PSA >0.1 mg ml⁻¹, and one patient with a locally advanced Gleason 5 + 5 who underwent a planned course of neoadjuvant ADT and adjuvant external radiation therapy (XRT) 6 months postprostatectomy. With a median followup time of 24 months, the rate of BCR excluding the two patients on ADT was 5%. This occurred in one patient with PSM, while the other did not. Both patients underwent salvage XRT at 14 months following prostatectomy with PSA levels now <0.01 ng ml⁻¹. The overall continence rate at 12 months was 86%, with an additional 4% on 1 pad per day, and 9% on 2 or more pads per day. Potency recovery was 58% of the 26 patients with preoperative potency at 12 months after surgery.

Utility of multi-parametric magnetic resonance imaging
Of the 25 patients who underwent multi-parametric MRI prior to RARP, the median interval from MRI to surgery was 6 weeks (IQR: 2–9). The addition of multi-parametric MRI improved clinical staging in

Table 1: Patient characteristics (n=44)

| Variables | Value |
|-----------|-------|
| Age (year), median (IQR) | 64 (57, 68) |
| BMI, median (IQR) | 28 (25, 31) |
| Age-adjusted Charlson comorbidity index, median (IQR) | 5 (4, 6) |
| Preoperative PSA, median (IQR) | 7.0 (5.2, 12.0) |
| Hospital stay (day), median (IQR) | 2 (1, 3) |
| Clinical stage (%) | |
| T1 | 18 |
| T2 | 48 |
| T3 | 34 |
| Biopsy Gleason score (%) | |
| 6 | 20 |
| 7 | 55 |
| 8–10 | 25 |
| Blood loss (ml), median (IQR) | 100 (50, 150) |
| Transfusion rate (%) | 0 |
| Pathology stage (%) | |
| T2 | 43 |
| T3 | 55 |
| T4 | 2 |
| Pathology Gleason score (%) | |
| 6 | 11 |
| 7 | 45 |
| 8–10 | 43 |
| PSM (%) | 14 |
| Lymph node excision (%) | 100 |
| Lymph node yield, median (IQR) | 9 (4, 13) |
| Lymph node positive (%) | 7 |
| Follow-up (months), median (IQR) | 24 (18, 32) |
| Biochemical recurrence (%) | 5 |
| Adjuvant therapy (%) | |
| Intermittent ADT | 2 |
| Neoadjuvant ADT and adjuvant XRT | 2 |
| Salvage XRT (%) | 4 |
| Continence, 12 months (%) | |
| 0 pads | 86 |
| 1 pads | 4 |
| 2 pads | 9 |
| Potency, 12 months (%) | 58 |

*a* Of 26 patient with preoperative potency. BMI: body mass index; ADT: androgen deprivation therapy; XRT: external radiation therapy; IQR: interquartile range; PSA: prostate-specific antigen; PSM: positive surgical margin
this subset of patients from 28% to 88%, predominantly by increasing detection of ECE (Table 2). Capsular involvement on MRI was found reliable in predicting pathologic ECE with a sensitivity 76.5% and specificity 71.4% (Table 3). ADC corresponds to the characteristics of the structural and magnetic environment that influences proton diffusion, and is lower in PCa than in benign tissue and inversely correlates with Gleason Grade. We analyzed 31 tumors in 22 patients with ADC values. In our series, ADCs discriminated Gleason Grade 8–10 adenocarcinoma with a median ADC of 857 microns s⁻¹, from Gleason 7 tumors with median ADC of 1153 μ² s⁻¹, and Gleason 6 tumors with a median ADC 1132 microns s⁻¹ (Table 4). The ADCs in Gleason Grade 8–10 was significant lower versus Gleason Grade 7 (P < 0.01) and 6 (P < 0.01).

Nerve sparing grade and functional outcomes
Only 26 patients with preoperative potency were included to evaluate NS and potency recovery, while all 44 patients were utilized to evaluate continence. At 12 months, patients with Group A (bilateral NS) correlated with 100% potency recovery, Group B (unilateral NS) experienced 80% potency recovery, and patients in Group D (non-NS) had 0% potency recovery. All patients were continent prior to surgery. At 12 months, the continence rate was 100%, 92%, 91%, and 50% for Group A to D, respectively. Although group sizes were small, we found the trend interesting. In Group A with only two patients, while potency and continence rates were 100%, PSM rate was also high at 100%, although no patient has yet to have BCR. In contrast, in Group D patients, there has been no potency recovery and only 50% of patients have complete continence, while the PSM rate in the non-NS group was 33%. PSM rates correlated with NS at 100%, 15%, 0%, and 33% for Groups A to D, respectively (Table 5).

Analysis of positive surgical margins
We have three cases of patients who underwent preoperative multi-parametric MRI with PSMs. In the first case, prostate needle biopsy revealed high-volume Gleason 5 + 4, while MRI confirmed high-risk disease with capsular involvement. Bilateral non-NS was performed with whole mount pathology revealing a 4.9 cm T3a adenocarcinoma, Grade IV NS bilaterally, and focal PSMs at the right anterior apex and left bladder neck (Table 6). The ADCs in Gleason Grade 8–10 was significant lower versus Gleason Grade 7 (P < 0.01) and 6 (P < 0.01).

Table 2: Staging shift (n=25)

| Stage (%) | Clinical stage | MRI stage | Pathologic stage |
|-----------|----------------|-----------|------------------|
| T1c       | 36             | 0         | 0                |
| T2a       | 28             | 8         | 4                |
| T2b       | 12             | 4         | 0                |
| T2c       | 20             | 28        | 28               |
| T3a       | 4              | 56        | 52               |
| T3b       | 0              | 4         | 12               |
| T4        | 0              | 0         | 4                |

Table 3: Comparison of ECE between pathology and MRI (n=25)

| MRI stage | ≥T3 | ≤T2 |
|-----------|-----|-----|
| ≥T3       | 13  | 2   |
| ≤T2       | 4   | 6   |

Table 4: Correlation between Gleason score and ADC (31 cancer lesions in 22 patients)

| Gleason score | ADC (microns² s⁻¹) |
|---------------|--------------------|
| 6             | 1132±258           |
| 7             | 1153±235           |
| 8–10          | 857±157            |

Table 5: Rate of potency recovery, continence and PSM

| NS groups | Potency recovery (%) | Continence (%) | PSM (%) |
|-----------|----------------------|----------------|---------|
| Bilateral | 100 (2/2)            | 100 (2/2)      | 100 (2/2) |
| Unilateral| 80 (8/10)            | 92 (12/13)     | 15 (2/13) |
| Partial   | 45 (5/11)            | 91 (21/23)     | 0 (0/23) |
| Non       | 0 (0/2)              | 50 (3/6)       | 33 (2/6) |

ADC: apparent diffusion coefficients

PSM: positive surgical margin; NS: nerve sparing

DISCUSSION
Despite the recent controversies in PSA screening and the emergence of active surveillance for selected patients, PCa remains the second leading cause of cancer death in men in the US. The identification of patients who will die from their PCa is critical. Albertsen et al. reported a higher probability in high-grade PCa patients of dying from PCa within 10 years of diagnosis when managed by observation or ADT alone. In the PCA Intervention Versus Observation Trial, after a median followup of 10 years, radical prostatectomy reduced mortality in the radical prostatectomy group among men with PSA > 10 ng ml⁻¹ (5.6% vs 12%, P < 0.02) and men with high-risk PCa (9.1% vs 17.5%) compared to the observation group.

With the adoption of robotic surgery for the treatment of PCa, RARP has been increasingly performed in high-risk patients. Recent reports describing the outcomes following RARP for high-risk disease have shown a PSM rate ranging from 23% to 54%, and with 24-month followup, and rates of BCR ranging from 13% to 47%,. Reported continence in the subset of high-risk patients range from 79% to 100%, while potency at 12 months range from 52% to 60%, respectively. Advantages of RARP compared to open radical prostatectomy include shorter hospital stays and decreased blood loss. In our series, we report favorable results with a 14% PSMs and a BCR rate of 6% excluding two patients treated with ADT. The continence rate was 86% and potency of 58% 12 months postprostatectomy. These results in our high-risk PCa population are consistent with other series and achieved with acceptable complications.

In this series, we selectively obtained multi-parametric prostate MRI for patients with high-volume disease on prostate biopsies and for patients we considered NS despite clinically palpable tumors. Digital rectal examination and PSA frequently under stage PCa and accurate staging has been reported as low as 8%. In contrast, staging accuracy of multi-parametric MRI range between 14.4% and 88%. We analyzed 31 tumors in 22 patients with ADC values.
and 100%,15,24,25 Roethke et al.3 have reported overall sensitivity and specificity for predicting ECE of 41.5% and 91.8% in 385 patients, respectively. In intermediate- to high-risk groups (PSA ≥10 ng ml⁻¹ and Gleason ≥7), MRI can be more effective in predicting ECE with sensitivity and specificity of 47.6% and 93.6%, respectively. In this study, the addition of MRI improved the accuracy of clinical staging from 28% to 88% inapplicable patients. In patients with pathologic T3a, the sensitivity and specificity of MRI to detect ECE was 76.5% and 71.4%, respectively. ADC values quantitate vascular capillary perfusion and can differentiate between lower- and high-risk PCa.8,15 We show mean ADCs in Gleason 8–10 PCs to be lower relative to Gleason 7 and Gleason 6 tumors. For high-risk PCs, the use of multi-parametric MRI may improve clinical staging and in particular predict the extent of ECE. This information can be used as an adjunct in conjunction with conventional parameters including Gleason Grade, PSA, findings on digital rectal exam, and intraoperative observations to optimize NS to preserve potency and continence while minimizing PSMs. McClure et al.18 have reported NS decisions changed in 27% of patients based on preoperative multi-parametric MRI.

The neurovascular bundle comprising of nerves, vessels, and adipose tissue is typically 3–5 mm in width and depth, allowing for graded NS depending on tumor involvement.3,20,27 Tewari et al.3 previously defined a grading system for NS based on whole mount pathology from I to IV, ranging from infrasfacial NS to no NS. In this classification, if the patients had different NS grades on either side of the prostate, the grades were classified according to the higher grade (lesser NS) of the two. We modified this grading system based on our microscopic review of whole mount slides to incorporate the NS variations we observed into four groups defined as: (a) bilateral NS, (b) unilateral NS, (c) partial NS, and (d) non-NS. Using this grading system, the extent of NS can be confirmed with pathologic whole mounts. Despite only two patients in Group A, our results suggest that bilateral NS may not be optimal for high-risk patients as we had a high-incidence of PSMs. Preoperatively we believed that both patients had clinical confined disease, neither with preoperative MRIs. With unilateral NS, partial NS, and non-NS, the return of continence and potency progressively decreased with generally fewer PSMs. Unilateral NS and partial NS, most commonly performed in our series, may balance acceptable oncologic and functional outcomes in high-risk patients. We did note 33% PSMs in our Group D patients, but this was due in part to extremely large bulky tumor volumes.

Table 6: Pathologic stage and NS results of patients with MRI and without MRI in high-risk PCA patients

| NS groups | MRI group | Non-MRI group |
|-----------|-----------|---------------|
| Pathologic stage |          |               |
| T2a       | 1         | 0             |
| T2b       | 0         | 1             |
| T2c       | 7         | 10            |
| T3a       | 13        | 8             |
| T3b       | 3         | 0             |
| T4        | 1         | 0             |
| Nerve sparing techniques | |               |
| Bilateral NS | 0         | 2             |
| Unilateral NS | 8         | 5             |
| Partial NS | 12        | 11            |
| Non-NS    | 5         | 1             |
| PSMs      |           |               |
| Bilateral NS | 0         | 2             |
| Unilateral NS | 1         | 1             |
| Partial NS | 0         | 0             |
| Non-NS    | 2         | 0             |

MRI: magnetic resonance imaging; NS: nerve sparing; PCa: prostate cancer; PSMs: positive surgical margins

This study has several limitations. First, it is a retrospective series with a small number of patients. Although a larger number would improve the statistical power when analyzing the predictive value of MRI or evaluating our modified NS grading system, we believe our trends and lessons are still applicable and awaiting validation with a larger cohort. Second, there was a strong selection bias in patients subject to MRI namely high-volume biopsy results or locally advanced disease based on physical findings, making the groups incomparable. Consistent with this bias, patients who underwent MRI in our series had relatively higher rates of pathologic T3 stage than patients without preoperative MRI. Finally, we have a relatively short follow-up time of 18 months. This is similar to other series, and we have adopted PSM, BCR, and utilization of adjuvant therapies as surrogates for oncologic outcomes in lieu of cancer-specific or overall survival.

AUTHOR CONTRIBUTIONS
JGW analyzed, interpreted the clinical data, and wrote the manuscript. JH reviewed pathological slides and revised the manuscript. AIC designed the study, analyzed the data, revised the manuscript, and supervised the project. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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