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ABSTRACT

Background: The Briganti updated nomogram (BN) is the most popular predictive model aiming to predict the presence of lymph node invasion (LNI) in patients with prostate cancer (PCa), but it lacks information obtained by preoperative imaging.
The primary aim of the study was to evaluate the role of multiparametric prostate magnetic resonance imaging (mp-MRI) in the indication to perform pelvic lymph nodes dissection (PLND) or not in patients with risk of LNI according to BN below 5%.
Methods:
Since March 2012 and September 2016, 310 patients who underwent a preoperative mp-MRI for staging purpose and subsequent robot-assisted extended PLND (RAEPLND) were retrospectively evaluated. mp-MRIs were prospectively analyzed by two experienced radiologists. The imaging parameters analyzed were the presence of extracapsular extension (ECE), seminal vesicles invasion (SVI) and predominant Gleason pattern 4 (pG4). All patients underwent RAEPLND by two experienced surgeons with a standardized technique. A dedicated uropathologist performed all pathological analysis. Univariate analysis and multivariate logistic regression analysis were used in order to identify the predictors of LNI in patients with PCa.
Results:
In the overall population, 57 (18.4%) patients had histologically proven pN1 disease. 48/250 patients (19.2%) with a risk of LNI >5% as calculated by the BN were staged pN1 at final histopathological analysis. 9/60 patients (15.0%) with a risk of LNI <5% as calculated by BN, who underwent RAEPLND anyway according to the findings at mp-MRI, were staged pN1 at final histopathological analysis. At multivariate logistic regression analysis, all the three mp-MRI parameters were significant independent predictors of LNI after RAEPLND.
Conclusions:
The role of mp-MRI seemed to be crucial in patients with a risk of LNI <5% as calculated by the BN. The presence of ECE, SVI or pG4 at mp-MRI was found to be an independent predictor of LNI by itself.

INTRODUCTION

Pelvic lymph nodes dissection (PLND) is considered the surgical standard for staging of prostate cancer (PCa).1 The rate of LNI varies from 5.8% for low, 10% for intermediate, and >25% for high risk groups, respectively.2 However, PLND can be associated with higher rates of complications such as lymphocele,3 thromboembolic events,4 ureteral, nerve, and vascular injuries, fever, and lymphedema that may result in longer hospital stay.5 PLND can be performed by open, pure laparoscopic, or robot-assisted approach. In the minimally invasive era, recent findings revealed that, thanks to the known advantages, robotic surgery could allow for a facilitated technique with potentially higher performance.6,7
Up to date, indications to PLND vary among the different scientific societies. Of note, the American Urological Association (AUA) guidelines consider that PLND should be reserved for patients with higher risk of LNI with no clear cut-off.8 On the other hand, European Association of Urology (EAU) guidelines recommends to performing PLND if the calculated probability of LNI based on the Briganti updated nomogram is over 5%.9 Conventionally PLND could be avoided in patients with a calculated risk below 5%.
A few number of predictive models aiming to predict the presence of LNI in patients with PCa is available in the literature. Among them, the Briganti updated nomogram is undoubtedly the most popular.
The nomogram was designed as including preoperative clinical and pathological variables but it lacks information obtained by preoperative imaging.10
The advent of the multiparametric prostate magnetic resonance imaging (mp-MRI), incorporating both anatomical and functional information, has improved the staging of PCa before surgery.11 The exam is able to inform the surgeon about the presence of eventual extracapsular extension (ECE) or seminal vesicles invasion (SVI);12,13 moreover, it offers the chance to predict tumor aggressiveness as calculated by the correlation between Diffusion Weighted Imaging (DWI) and predominant Gleason pattern 4 (pG4).14 Even if the above-mentioned information are not included in the Briganti updated nomogram, they could influence the choice of the surgeon refining PCa staging.

The primary aim of the study was to evaluate the role of mp-MRI in the indication to perform PLND or not in patients with risk of LNI according to Briganti updated nomogram below 5%. The secondary aim was to identify independent predictors of LNI among the suspicious findings at mp-MRI.

MATERIALS AND METHODS

Study population

Since March 2012 and September 2016, 527 patients underwent preoperative mp-MRI for staging purpose prior to radical prostatectomy. Among them, 320 underwent robot-assisted extended PLND (RAEPLND). Ten patients were discarded due to finding at preoperative staging with CT-scan or MR imaging of lymph nodes suspected for cancer. A total of 310 patients were extracted from our institutional database dedicated to robot-assisted surgery for PCa and retrospectively analyzed for the purpose of the study.

Multiparametric MRI

All analyzed patients underwent preoperative mp-MRI according to the ESUR guidelines. PIRADS 1.0 classification was used for each described lesion.15 mp-MRIs were performed at two centers: center 1) 1.5-T scanner (Signa Excite HD, GE Healthcare) using a 4-channel phase array coil combined with an endorectal coil (Medrad, Warrendale); center 2) 1.5-T scanner (Achieva HD, Philips Healthcare) using a 5-channel phase array coil combined with an endorectal coil (Medrad, Warrendale). Procedures were performed at least 6 weeks after prostate biopsy in order to minimize post-biopsy artifacts. The imaging protocol consisted of triplanar T2-weighted fast spin-echo sequences, DWIs in transverse planes at different b-values and DCE after injection of contrast agent. All magnetic resonance images were sent to a workstation and post-processed (Functool v. 9.4.05a, GE Healthcare, and Intellispace Portal v. 6.0.3.12200, Philips Healthcare). A detailed description of mp-MRI acquisition and the post processing of images has been reported in the Supplementary Material.15-17 Two experienced radiologists had prospectively analyzed mp-MRIs during their regular clinical assignment to the magnetic resonance service. The diagnostic features of malignancy on magnetic resonance images were previously described18 and reported in the Supplementary Material.
For the purpose of the study, ECE was defined as irregular bulging of the prostatic capsule, asymmetry of the neurovascular bundle and/or presence of tumor out of the capsule or periprostatic tissue. SVI was defined as the presence of a hypointense lesion in one or both seminal vesicles. As based on the previously reported correlation between ADC and Gleason score,14 the criterion for the risk of pG4 was the finding of very low apparent diffusion coefficient (ADC) values (<0.8 for center 1, <0.6 for center 2) in the peripheral zone lesions.

Robot-assisted extended pelvic lymph nodes dissection (RAEPLND)

All patients underwent robot-assisted radical prostatectomy and RAEPLND by two experienced surgeons by using da Vinci® SiHD robotic system (four arms configuration). The step-by-step technique was previously described.19 Briefly, all the procedures were performed by a transperitoneal approach. The lymph nodes dissection included the lymphatic packages located at the distal tract of the common iliac artery, the medial portion of the external iliac artery, the external iliac vein and the internal iliac vessels, and along the obturator nerve and the presacral space (Fig. 1).

Histopathological analysis

A dedicated uropathologist performed all the histopathological analysis. The tissue was submitted for permanent sectioning. The pathologic workup to detect lymph nodes, as well as the lymph nodal metastases, included direct visualization, palpation and standard hematoxylin-eosin staining.

Statistical analysis

The descriptive statistics of patients' characteristics were reported as median (interquartile range, IQR) for continuous variables, whilst as frequency (percentage) for categorical ones. Whether the decision to undergone a RAEPLND changed on the basis of findings at mp-MRI was assigned as a binary variable. Univariate analysis and multivariate logistic regression analysis were used in order to identify the predictors of LNI in patients with PCa.

RESULTS

Patients' clinical and pathological characteristics were reported in Table 1. A total of 8031 lymph nodes was harvested with a median number of 26 (IQR 20-32) lymph nodes per patient. Fifty-seven (57/310,18.4%) patients had histologically proven pN1 disease. The total number of metastatic nodes was 147 with a median number of 3 (IQR 1-4) positive lymph nodes per patient.
By mp-MRI ECE was diagnosed in 202 (65.2%) patients, SVI in 58 (18.7%) patients and pG4 in 211 (68.1%) patients. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of mp-MRI parameters (ECE, SVI, and pG4) for predicting LNI were reported in Table 2.

Two-hundred fifty patients (250/310, 80.6%) with a risk of LNI >5% as calculated by the Briganti updated nomogram underwent RAEPLND. Forty-eight patients (48/250, 19.2%) were staged pN1 at final histopathological analysis.
Sixty patients with a risk of LNI <5% as calculated by Briganti updated nomogram (60/310, 19.4%) underwent RAEPLND anyway according to the findings at mp-MRI (Fig. 2). In this group of patients, the rate of pN1 stage was 15.0% (9/60).
At univariate analysis, considering age, indication to perform PLND according to BN, and the three mp-MRI parameters, only the imaging parameters were significantly associated with the presence of nodal metastasis (p=0.001, p<0.001, and p=0.002 for ECE, SVI, and pG4, respectively).
Finally, at multivariate logistic regression analysis, all the three mp-MRI parameters were significant independent predictors of LNI after RAEPLND: the odds ratio (OR) of ECE, SVI and pG4 were 2.82 (95% CI 1.30-6.14), 3.44 (95% CI 1.76-6.72) and 2.30 (95% CI 1.09-5.28), respectively.

DISCUSSION

Several predicting tables and nomograms have been created aimed to decide if performing PLND or not on the basis of the risk of LNI. The majority of them was developed and validated in the cohort of patients who underwent limited PLND.
A very popular one is the Memorial Sloan Kettering Cancer Center (MSKCC)-LNI-cores nomogram20 that can be used to decide when to perform a lymphadenectomy at the time of RP.
Briganti et al. were the first group to develop a nomogram for preoperative prediction of LNI in patients with PCa who underwent extended PLND.21
The factors found to be associated with LNI at final histopathological analysis were clinical stage, serum PSA and biopsy Gleason score, giving the nomogram an accuracy of 76%. The nomogram was updated in 2012 with data about tumor volume by adding the percentage of positive cores at prostate biopsy to the originally considered factors.10 However, the clinical parameters considered could underestimate the risk of LNI, primarily due to the fact that the information obtained by imaging is lacking.
In this context, both computerized tomography (CT) scan and MRI demonstrate a poor performance in the detection of lymph node metastases in patients with PCa, probably because the definition of nodal metastasis on imaging relies on size criteria. As reported by a meta-analysis in 2008, the pooled sensitivity of MRI is 0.39 and the pooled specificity 0.82.22 In recent years, promising new functional imaging modalities such as choline positron emission tomography (PET)-CT scan have been introduced to visualize nodal metastases.23 These techniques have not yet widely diffused due to the high costs and limited accessibility for the majority of patients.
More recently, the advent of mp-MRI offered the advantage of obtaining information on both the anatomy of the prostate gland and its functional behavior. In a recent study on 112 patients, the Authors concluded that the use of mp-MRI resulted in improved accuracy of existing nomograms for prediction of ECE at final pathology. In particular, the AUC increased from 0.85 to 0.92 and from 0.86 to 0.94, when mp-MRI was added to Partin tables or Memorial Sloan-Kettering nomogram, respectively.24 Our group already reported that mp-MRI seems to provide more information if compared to prostate biopsy, thus allowing for a better PCa staging.25 Moreover, Thoeny et al. recently reported that DWI could predict the LNI of normal-sized pelvic lymph nodes in patients with PCa.26 Nevertheless, a high false-negative rate is still a limitation for the widespread use of DWI alone.
The findings of the present study seemed to confirm the role of some findings at mp-MRI in expanding the indication to RAEPLA even in patients with risk of LNI as calculated by the BN <5%.
In the multivariate logistic regression analysis, the presence of ECE, SVI or pG4 on mp-MRI were significant independent predictors of LNI. SVI was the most significant parameter, showing a risk of LNI 3.4 fold higher when detected at imaging.
We highlight the role of mp-MRI in patients with a risk of LNI <5% as calculated by the BN. In this selected population, the histopathological analysis showed lymph node metastases in 9/60 (15.0%) patients. The rate was not statistically different with respect to the overall rate of pN1 patients of the cohort of patients who underwent RAEPLND according to Briganti calculated risk of LNI >5% (19.2%, p = NS), suggesting that the mp-MRI could be helpful in detecting patients with risk of LNI according to BN <5% harboring nodal metastases.
The study was not devoid of limitations: first, the retrospective fashion which was conducted by; second, the sample size should be increased in order to confirm the findings; third, the inclusion of two centers expertise in performing mp-MRI could have generated an inter-observer variability in interpreting imaging findings that were not tested. On the other side, we believe this could be translated in a merit of the study, allowing for better reproducibility.
The use of two different MRI scanners and thus respective ADC cut-offs to determine the pG4 in peripheral zone lesions could represent another matter of debate. To overcome this potential limit, an expert uro-radiologist (F.R.) retrospectively calculated the ADC ratio for each selected patient, as reported in a recently published paper.27 By

using this parameter in addition to ECE and SVI instead of the ADC, the patients with a risk of LNI <5% as calculated by the BN who were candidate to RAEPLND would have been the same (data not shown).
The message of the present study was to suggest that some findings at mp-MRI can expand the indication to RAEPLND in patients with a risk of LNI as calculated by BN below 5%. We underline that in this study, all RAEPLNDs were performed by experienced surgeons using a standardized extended template, with a high median number of dissected lymph nodes. Moreover, all the harvested lymph nodes were analyzed by an expertise dedicated uropathologist. Of note, all mp-MRI studies were performed prior to surgery, for staging and/or tailoring of nerve-sparing approaches, without adding extra costs by imaging for nodal staging.
In conclusion, in our experience, some information derived from mp-MRI could expand the indication to RAEPLND. The role of mp-MRI seemed to be crucial in patients with a risk of LNI <5% as calculated by the Briganti updated nomogram. Moreover, the presence of ECE, SVI or pG4 at mp-MRI was found to be an independent predictor of LNI by itself. Larger sample size would definitely confirm our data and define the exact role of mp-MRI in this scenario.

Supplementary information is available at PCAN's website.

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CONFLICT OF INTEREST STATEMENT
All the Authors certify that they have nothing to disclose.
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