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ABSTRACT

BACKGROUND
In the era of mpMRI guided target fusion biopsy (FB), the role of concomitant standard biopsy (SB) in naïve patients still remains under scrutiny. The aim of this study was to compare the detection rate (DR) of clinically significant prostate cancer (csPCa) in biopsy naïve patients with positive mpMRI who underwent FB alone (Arm A) vs FB+SB (Arm B). Secondary objectives were to compare the incidence of complications, the overall PCa DR and the biopsy results with final pathological findings after robotic prostatectomy (RARP).

METHODS
This is a single center prospective non-inferiority parallel two arms (1:1) randomized control trial (ISRCTN registry number ISRCTN60263108) which took place at San Luigi Gonzaga University Hospital, Orbassano (Turin, Italy) from 4/2019 to 10/2021. Eligible participants were all adults aged<75 years old, biopsy naïve, with serum PSA<15 ng/mL and positive mpMRI (Pi-Rads V.2>3). FB was performed under ultrasound guidance using the BioJet fusion system; four to six target samples were obtained for each index lesion. SB was performed in accordance with the protocol by Rodríguez-Covarrubias. RARP with total anatomical reconstruction was carried out when indicated. DR of PCa and csPCA (Gleason Score >7) were evaluated. Post-biopsy complications according to Clavien-Dindo were recorded. Concordance between biopsy and RARP pathological findings was evaluated. Fisher's Exact test and Mann–Whitney test were applied; furthermore, Logistic Principal Component Analysis (LogPCA) and Pearson's correlation method, in terms of correlation funnel plots, were performed to explore data in a multivariate way.

RESULTS
201 and 193 patients were enrolled in Arm A and B, respectively. csPCa DR was 60.2% *vs.* 60.6% in Arm A and B respectively (Δ 0.4%; P=0.93); whilst overall PCa DR was 63.7% *vs.* 71.0% (Δ 7.3%; P=0.12). However, in a target only setting, the addition of SB homolaterally to the index lesion reaching a non-inferior performance compared to the combined sampling (Δ PCa DR 3%). Although the differences of 7.3% in PCa DR, during RARP were registered similar nerve sparing rate (P=0.89), positive surgical margins (P=0.67) and rate of significant upgrading (P=0.12). LogPCA model showed no distinction between the two cohorts; and Pearson's correlation values turned to be between -0.5 and +0.5. In Arm B, the lesion diameter <10 mm is the only predictive variable of positive SB only for PCa (P=0.04), with an additional value +3% for PCa DR.

CONCLUSIONS
In biopsy naïve patients, FB alone is not inferior to FB+SB in detecting csPCa (Δ csPCa DR 0.4%). Δ 7.3% in overall PCa DR was registered between the two Arms, however the addition of further standard samples homolaterally to mp-MRI index lesion improved the overall PCa DR of FB only sampling (Δ PCa DR 3%). The omission of SB did not influence the post-surgical outcomes in terms of NS approach, PSMr and upgrading/downgrading.

Key words: Prostatic neoplasms; Multiparametric magnetic resonance imaging; Biopsy; Prostatectomy; Robotics.

In the last years, with the aim to improve prostate cancer (PCa) diagnostic pathway, different tools have been introduced, such as novel biomarkers or risk calculators.[1, 2] However, the real game changer has been the advent of multiparametric magnetic resonance imaging (mpMRI), which has rapidly entered in urological guidelines both in biopsy naïve or re-biopsy setting.[3]
Thanks to the technological development, it is currently possible to perform a fusion biopsy with a real time merging of mpMRI slices and transrectal ultrasound (TRUS) images, performing a fusion biopsy (FB) procedure.
Even if the latest EAU guidelines recommend the combination of FB and standard biopsy (SB) in biopsy naïve patients,[3] the real added value of random samples is controversial.
In fact, the majority of the published experiences report that from 9% to 15% of clinically significant PCa (csPCa) can be missed when performing FB alone,[4] showing a greater detection rate (DR) with a combined approach.[5-7] On the contrary, recently published series in high volume centers revealed a non-significant increase in the DR when SB was added.[8, 9]
Furthermore, the achievement of concordance between biopsy findings and final pathological results after radical prostatectomy is fundamental[9, 10] since patients' treatment tailoring is based on biopsy findings.
The aim of this prospective non-inferiority randomized study was to compare, in naïve patients with positive mpMRI, the DR of csPCa in a diagnostic pathway based on FB alone *vs.* a diagnostic process based on FB plus SB.

MATERIALS AND METHODS

The following section has been reported in accordance with CONSORT statement to trial of nonpharmacologic treatment.[11]

Trial design

This is a single center prospective non-inferiority parallel two arms randomized control trial (1:1 for two arms) for patients with suspicious PCa and positive mpMRI who were not submitted to prior prostate biopsy. The trial was registered on ISRCTN registry (registry number ISRCTN60263108).

Participants

Eligible participants were all adults aged <75 years old, biopsy naïve, with serum PSA<15 ng/mL, and positive mp-MRI (PI-RADS V.2>3[12]). Exclusion criteria were contraindication to prostate biopsy (*i.e.* inability to stop anticoagulant therapy).

Study setting

The study took place at San Luigi Gonzaga University Hospital, Orbassano (Turin, Italy) from April 2019 to October 2021. This study was approved by our local ethical committee (protocol N. 14/2019) and patients signed an informed written consent.

Intervention

Enrolled patients were randomly submitted to FB alone (Arm A) *vs.* FB+SB (Arm B).
All the participants had a suspicion of PCa (see section "Participants") and previously underwent mpMRI performed according to PI-RADS Guidelines.[13] Positive mpMRI was defined as the presence of a Pi-Rads v.2>3 lesion, as determined by EAU Guidelines.[3] In case of multiple PI-RADS >3 lesions, specifically for this study, stratification and analyses were focused on the index lesion only.[14] All mpMRI that were not performed in referral centres were then re-evaluated with an experienced radiologist before biopsy's execution, in particular for small and indeterminate lesions.
As recommended by EAU urological guidelines, all patients were submitted to prostate biopsy in an ambulatory setting;[3] all the operators were already experienced in this procedure.[15] A Hawk Ultrasound scanner 2102 EXL with a biplanar transducer (B-K Medical, Herlev, Denmark) was used to

carry out the TRUS. Biopsy samples were obtained with a disposable 18-gauge biopsy gun; the specimen size was 18-22 mm (Bard Medical, Covington, GA, USA).
As we previously published, FB was performed using the BioJet fusion system (D&K Technologies, Barum, Germany).[16] On mpMRI images, the regions of interest (ROIs) and the whole gland were previously manually contoured. Then, during the procedure, in real time, prostate and ROIs contours were overlapped with the TRUS image. Antibiotics prophylaxis was administered according to EAU Guidelines.[3] The procedure was carried out with patients in a lithotomic position and, based on lesion's location, an 18 or 42 degrees transrectal needle guide was used for posterior lesions and transitional zone/lateral lesions, respectively.
For lesions in anterior zone, a transperineal approach was adopted.
Four to six target samples were obtained for each FB based on lesion's extension and our previously published experience.[17]
According to the protocol by Rodríguez-Covarrubias *et al.*, in Arm B patients, SB was carried out with a transrectal approach obtaining 12 cores,[18] by a second urologists blinded to mpMRI findings. For secondary endpoint assessment, in case of positive biopsy and in accordance with EAU guidelines, after a multidisciplinary team discussion (MDT), active surveillance, radiotherapy or radical prostatectomy were proposed to patients. Those who opted for surgical intervention were submitted to robot-assisted-radical-prostatectomy (RARP) with or without extended pelvic lymphnode dissection (ePLND), following our previously published technique.[19]

Outcomes
The primary objective of the study was to compare, in biopsy naïve patients with positive mpMRI, the DR of csPCa in patients enrolled in Arm A *vs.* Arm B.
Secondary objectives of the study were:
1. to compare the overall DR of a diagnostic pathway based on FB alone *vs.* a diagnostic process based on FB sampling plus random sampling;
2. to evaluate the role of additional SB sampling (in terms of tumor characteristics and side);
3. to compare the incidence of complications in the two diagnostic pathways;
4. to compare the whole mount histopathological findings after RARP with biopsy findings in both study groups.

Sample size
Considering rates of 40% in Arm A, with an expected rate of 55% in Arm B, a non-inferiority margin of 5% in according to previous findings,[6, 7] to reach a power of 80% with a two-sided type I error equal to 0.05, 154 patients for each group are needed.[20] In order to take into account a possible 10% loss at follow up, we planned to enroll a total number of 170 patients for each group (340 in total). The sample size calculation was performed with ADDPLAN® (ADDPLAN 6.1.1, Inc., an Aptiv Solutions company. ADDPLAN GmbH D-50739, Germany).

Randomization (sequence generation)
Patients were allocated in the two arms by a stratified randomization by site, age (< or ≥70), PSA (< or ≥10), PIRADS (= or >3) and positive/negative digital rectal examination. An Excel macro was created in order to assign dynamically each patient to the arms.

Data collection
Biopsy Gleason score (GS), number of total and positive cores, total and maximum cancer core length (CCL) and maximum cancer core invasion (CCI) rate were acquired in accordance to the standards of reporting for MRI targeted biopsy studies (START) criteria.[21] csPCa was defined as biopsy GS ≥ ISUP 2 or maximum CCL≥5 mm.[22, 23] The added value of SB was evaluated analyzing the results of the entire mapping but also assessing the role of sole standard sampling homolaterally to mpMRI index lesion.

An expert uropathologist (EB) analyzed the specimens and was blinded to patients' enrollment for this study or not.
Prostate specimen from patients who underwent RARP were chosen as reference standard. The organ processing was executed following the aforementioned technique, subsequently calculating GS and ISUP grade for each lesion found.[24] 30-days biopsy related complications were classified according to the Clavien-Dindo Classification.[25] The DR was defined as the ratio between the total cases of PC/csPCa diagnosed thanks to a particular biopsy (FB, FB+SB or SB) and the total number of patients. In addition, PI-RADS score was considered to perform further classifications.

Statistical analysis
Continuous and categorical variables were reported as mean and standard deviation or frequencies and percentages as appropriate. Mean with interquartile range (IQR) for continuous variables and frequencies for categorical ones were reported.
The comparisons between groups were done using the Fisher's Exact Test for categorical variables and the Mann–Whitney test for continuous ones; McNemar's Test was used to compare DR Furthermore, a Machine Learning approach such as Logistic Principal Component Analysis (LogPCA) was performed on the binarized data to explore data in a multivariate way.[26] Lastly, Pearson's correlation method, in terms of correlation funnel plots, were performed. Finally, a multivariate logistic regression (MLR) analysis assessing the association between pre-biopsy parameters and detection of PCa by SB alone (*i.e.* with negative FB) was built. This analysis considered four variables: prostate volume, PSA serum levels, lesion diameter (> or<than 10mm) and PI-RADS score (divided in <3 and >3).
All the statistical tests were carried out considering a type-I error alpha= 5%. These analyses were performed with Jamovi 2.0 software and R Statistic Software 3.6.1.

RESULTS

Participant flow
Four hundred and five patients were eligible for enrollment. Among them, 8 were excluded for their choice; 397 were then randomized; 201 were enrolled in Arm A and 196 in Arm B. Among the latter, 3 were excluded from the analysis due to intolerance during SB sampling. None were lost at follow-up during the first 12 months after biopsy. 110 patients underwent RARP (58 in Arm A and 52 in Arm B) (Supplementary Digital Material 1: Supplementary Figure 1). No protocol deviations were recorded.

Baseline data and numbers analyzed
Patients' pre-biopsy baseline variables were comparable between the two groups as shown in Supplementary Digital Material 2, Supplementary Table I. In particular, no differences were found in terms of Pi-Rads v.2 score (P= 0.06), lesion volume (P= 0.49), MRI lesions characteristics and PSA density (P= 0.26) (Supplementary Digital Material 3, Supplementary Table II). The enrolled patients, apart from 3, were analyzed for primary endpoint and secondary endpoints n°1, n°2 and n°3. For secondary endpoint n°4, only patients who underwent RARP were included in the analysis (27.9% of the entire population; 29.8% and 25.8% of Arm A and B, respectively). Demographic variables were reported in Supplementary Digital Material 4, Supplementary Table III.

Evaluation of PCa and csPCa DR
As shown in Table I no differences were found in terms of PCa and csPCa DR in the two Arms (DR PCa 63.7% *vs.* 71.0% in Arm A and B respectively, mean difference (Arm B-A): -7.3%, 95%CI -23.5% -8.9%; P=0.12. DR csPCa 60.2% vs 60.6%, mean difference (Arm B-A) 0.4%, 95%CI -15.7% -14.9%; P=0.93). Also after a stratification according to lesions' PIRADS score PCa and csPCA DR were comparable (Table I). Furthermore, the histopathological findings were comparable in terms of GS (P=0.08), Total

CCL (P=0.06), Maximum CCL (P=0.67) and Maximum CCL rate (P=0.11), see Supplementary Digital Material 5, Supplementary Table IV. Then, analyzing the role of the additional SB sampling homolaterally to mp-MRI index lesion (in terms of tumors' characteristics revealed with SB), only 3% of discrepancies between PCa DR of the two arms were revealed (128/201 [63.7%] *vs.* 129/193 [66.8%] in Arm A and B respectively; P=0.51); whilst difference in csPCa was 121/201 (60.2%) *vs.* 115/193 (59.6%), P=0.90.

Evaluation of post-biopsy complications

No differences were found between the two Arms in terms of infectious, hemorrhagic and micturition complications. The occurrence of complications stratified according Clavien-Dindo was similar (P=1); see Supplementary Digital Material 6, Supplementary Table V. All the OR at logistic model were not significant (95% CIs include 1), *i.e.* no differences in complications were recorded in the two groups (Supplementary Digital Material 7, Supplementary Table VI).

Analysis of post-RARP findings

The different type of biopsy approach does not influence the NS approach during RARP (P=0.89), and the PSMr was similar (P=0.67).

Similar rates of upgrading and downgrading were recorded (P=0.052 and 0.84 respectively); with a rate of upgrading and subsequent change of risk group of 12.1% and 23.1% (P=0.12) in Arm A and B respectively. Specifically for Arm B, only in 4 (7.6%) cases a significant upgrading (with change of risk group according to D'Amico) was recorded thanks to SB only.

Focusing on final pathology index lesion's location, in 87.9% of the patients in Arm A and 88.5% in Arm B (P=0.98) it was homolateral to MRI index lesion; in case of discordance, in all the cases csPCa was found. The sub-analysis of Arm B patients revealed that only in 4 cases (7.6%) the index lesion after RARP was contralateral to MRI index lesion but homolateral to SB index lesion (Table II).

Correlation studies and Logistic Principal Component Analysis

LogPCA model was computed on the overall cohort showing no graphical differences between the arms. In fact, Figure 1A showed no distinction between the two cohorts since the clusters of the two Arms are overlapped. These results were verified by Pearson's correlation values and correlation funnel (Figure 1B): all the correlation values turned to be between -0.5 and +0.5, thus indicating no significant relation between the two arms.

Then, focusing on operated patients, again LogPCA showed no discrepancies between the two arms, and the Pearson's correlation values with correlation funnel indicated similar surgical outcomes (in terms of NS rate, PSMr, final pathology upgrade/downgrade) despite the different biopsy approach (Figure 1C, D).

Multivariable logistic regression model

Our data revealed that Arm B had a PCa DR 7.3% higher than Arm A (P=0.12). Specifically for Arm B, SB was positive in 20 patients (10.3%) and only 14 (7.2%) had csPCa.

At MLR analysis, lesions' diameter lower than 10mm (OR: 3.84; CI 95% 1.04 14.08; P=0.04) seemed to be the only predictive variable of positive SB only (Supplementary Digital Material 8, Supplementary Table VII). No variables were found to be predictive of positive csPCa at SB only.

DISCUSSION

To the best of our knowledge, herein we report the first prospective RCT comparing FB alone *vs.* a combined approach with FB and SB in biopsy naïve patients.

This study was designed in accordance with good clinical practice guidelines and following the concept of precision medicine.[27] Thanks to new technologies (such as mpMRI and FB platforms) it is

indeed possible to offer to our patients a tailored approach, omitting diagnostic procedures potentially not impacting disease management and patient history, with related risks of overtreatment and morbidities.

In the last years the diagnostic pathway of PCa changed from the introduction of mpMRI, with the recent recommendation by EAU guidelines panel[3] to perform a combination of FB and SB based on high level previously published Literature.[28]

However, few retrospective experiences started to pave the way for a FB alone approach[8] in biopsy naïve patients.

In the current study, prospectively and after a 1:1 randomization, no differences were found in terms of PCa and csPCa DR in the two arms, despite the addition of SB (DR PCa 63.7% *vs.* 71.0%, P=0.12; DR csPCa 60.2% *vs.* 60.6%, P=0.93 in Arm A and Arm B respectively) satisfying our primary endpoint and n°1 secondary endpoint. These data were supported by the LogPCA model applied, aiming to investigate the variability in the collected data to discover any cluster or similarities among the patients. In the present cases, patients of Arms A and B did not show any significant difference or correlation since no clusters were observed in the LogPCA Scores Plots and no parameters showed absolute Pearson's correlation values higher than 0.5.

However, the open question, as mentioned in our n°2 secondary endpoint, still remains: who are the patients deserving SB? In Arm B cohort, we observed that in case of negative FB despite a positive mpMRI, 10.3% and 7.2% of PCa and csPCA were diagnosed with SB only.

Among them, three patients only had a lesion diameter >10 mm. In fact, trying to identify the best candidate requiring the addition of SB, our MLR model, notwithstanding the low sample size, revealed that patients with negative FB and lesion diameter <10 mm deserve the addition of SB due to a high risk of missed PCa. A possible reason could be found in the more challenging setting for FB to correctly identify small lesions. In current Literature this issue still remains debated,[29] however, some recently published experiences showed how the real added value of SB is limited in patients with small lesions and highly suspicious mpMRI.[30]

Thus, with the addition of SB have we obtained some more clinically relevant information on patients' PCa?

Firstly, we denote that among the 87 patients with both FB and SB positive sampling in Arm B, 7 patients (8%) were upgraded (in terms of ISUP grade) at SB with only 5 patients (5.7%) upgraded with change of the risk class, suggesting the low impact of SB in disease management.

Moreover, focusing on the 20 patients with positive SB only (with negative FB), the concordance rate (homolateral to index lesion) between positive cores at SB and mpMRI index lesion was 80% (16/20) (Table III). Furthermore, in 6/8 (75%) patients who underwent RARP on the basis of SB findings only, the mpMRI and whole mount histopathological index lesion corresponded in terms of laterality and location.

Analyzing these data, it seems reasonable, especially in patients with a small mpMRI index lesion, (<10 mm) to perform an ipsilateral standard sampling, as already suggested by some authors[31] or a saturation target biopsy homolaterally to the index lesion, as reported by other authors.[32] In fact, in our series, the addition of homolateral SB determines a difference of only 3% in terms of PCa DR between the two Arms, limiting the role of contralateral standard sampling (63.7% *vs.* 66.8%; P=0.51).

On the other hand, the addition of contralateral standard sampling in our cohort led to the diagnosis of just 4/193 patients (2%) with csPCa.

Therefore, we can speculate that the execution of SB homolaterally to the index lesion decreases the additional value of standard sampling from 7.3% (DR PCa 128/201 Arm A *vs.* 137/193 Arm B composed by FB and complete SB) to 3% (DR PCa 128/201 Arm A *vs.* 129/193 Arm B composed by FB and homolateral SB only), bringing the risk of losing a PCa only 4.2% higher than the "gold standard" combined approach. These additional samples allow to reach a non-inferiority performance (Δ<5%) of the two different approaches for overall PCa DR as estimated in section "Sample size."

Furthermore, we would emphasize that the differences in terms of csPCa DR was not influenced by the addition of homolateral SB (Δ 0.6%) (Table IV).
Focusing on our n°3 secondary endpoint the complication rates were similar between the two Arms in terms of post-biopsy Clavien Dindo complications (P=1) and as showed at logistic model stratified for different type of complications (all the OR are not significant; 95%CIs include 1).
Lastly, analyzing our n°4 secondary endpoint, another strength of our study is represented by the analysis of the sub-cohort of patients who underwent RARP in both Arms, comparing final pathology with biopsy results, even if it might have been affected by the underpowered sample size. Our findings revealed that the addition of SB did not change the surgical approach or pathological findings, in fact the rate and side of NS approach was similar between the two arms (P=0.89 and P=0.37 respectively); furthermore, the occurrence of PSM (that is related to NS approach and the knowledge of tumor's location) was similar (P=0.67).
Considering histopathological findings, the rate of upgrade and downgrade with change of risk class at final pathology after RARP was not influenced by the addition of SB (P=0.12 and P=0.65), proving the good capability of FB alone to correctly define PCa's aggressiveness. In fact, among the 34 operated patients in Arm B with both FB and SB positive, an upgrading with risk group change compared to FB or SB or FB+SB characterization was recorded in 4 (11.8%), 7 (20.6%) and 4 (11.8%) cases (P=0.49). Moreover, the concordance rate between biopsy and pathological ISUP grade was similar between the two Arms (44/58 *vs.* 31/52 P=0.06).
Lastly, it is interesting to denote that the side of the index lesion at final pathology corresponded to MRI index lesion in 88% of the cases, confirming the evidence supporting the role of mp-MRI in PCa identification.

Limitations of the study

All these considerations suggest how the tumor characterization is mostly driven by FB sampling on the target area, and it is in line with what was recently speculated by Kasivisvanathan *et al.*:[30] Authors confirmed that tumors identified with SB alone have a different, and less aggressive natural history and features in comparison with the ones identified by FB in the target area.
Nevertheless, we would like to underline that secondary endpoint results are partially affected by the sample size, which was calculated on the base of the primary endpoint (DR csPCa). Secondary endpoint results must then be observed considering this issue, suggesting the necessity of further studies in order to evaluate each of these other outcomes.
Moreover, other limitations can be mentioned: we think that the high experience of radiologists, pathologists and urologists who evaluated and performed mpMRIs and biopsies may have led to a maximization of FB performance, with a possible lack of reproducibility in other centers.
In addition, as previously stated, some comparisons between the subgroups might have been less reliable due to the small sample size; furthermore, the missing of whole-mount histopathological findings in patients with negative biopsy does not allow to know the false negative rate. Lastly, this is a single center experience: future multicenter studies will help to corroborate these results.

Conclusions

In biopsy naïve patients, 7.3% of PCa are missed by FB alone approach respect to FB+SB.
However, the addition of further standard samples only homolaterally to FB and mp-MRI index lesion, improves the DR of biopsy sampling, reaching a non-inferior performance compared to the standard combined one (only 3% of PCa are missed).
Focusing on csPCA DR, no differences were recorded between FB vs FB+SB (only 0.4% csPCa are missed).
Moreover, FB only seems to be adequate to drive the surgical intervention, showing comparable pathological findings and surgical outcomes in terms of NS rate and PSMr.

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TABLE I. Comparison of cancer detection rates in terms of allocation arm and biopsy approach, also stratified for PiRads Score.

	Arm A (FB) (201 pts)	Arm B (FB+SB) (193 pts)		P value
Overall detection rate of PCa, number (%)	128 (63.7)	137 (71.0)		0.12
	FB	FB	SB	Arm A *vs.* FB Arm B 0.53 Arm A *vs.* SB Arm B 0.09 Arm B FB *vs.* Arm B SB 0.30
	128 (63.7)	117 (60.6)	107 (55.4)	
Overall detection rate of csPCa, number (%)	121 (60.2)	117 (60.6)		0.93
	FB	FB	SB	Arm A *vs.* FB Arm B 0.17 Arm A *vs.* SB Arm B 0.001 Arm B FB *vs.* Arm B SB 0.18
	121 (60.2)	103 (53.3)	90 (46.6)	
Ratio of overall detection of csPCa/PCa, %	94.5	85.4		(Cohen's Kappa=0.46 [0.36-0.59])
Overall detection rate of PCa at SB only, number (%)	NA	20 (10.3)		
Overall detection rate of csPCa at SB only, number (%)	NA	14 (7.2)		
Ratio of overall detection of csPCa/PCa, %	NA	70.0		
PiRads Score stratification				
	Arm A (201 pts)	Arm B (193 pts)		P value
Pirads 3 DR, number (%)				
• PCa • csPCa	12 (28.6) 9 (21.4)	26 (46.4) 19 (33.9)		0.073 0.17
Pirads 4 DR, number (%)				
• PCa • csPCa	72 (66.7) 69 (63.9)	69 (62.7) 62 (56.4)		0.54 0.25
Pirads 5 DR, number (%)				
• PCa • csPCa	45 (88.2) 44 (86.3)	22 (81.5) 22 (81.5)		0.41 0.57

PCa: prostate cancer; csPCa: clinical significant prostate cancer; FB: fusion biopsy; SB: standard biopsy; DR: detection rate.

Table II. Surgical and pathological variables after radical prostatectomy and rate of reclassification by downgraded and upgraded on prostatectomy whole-mount histopathology by biopsy method.

	Arm A (58 pts)	Arm B (52 pts)	P value
Lymphadenectomy, N. (%)	51 (87.9)	44 (84.6)	0.61
Nerve sparing			
None Monolateral Bilateral	12 (20.7) 8 (13.8) 38 (65.5)	9 (17.3) 8 (15.4) 35 (67.3)	0.89
• Full bilateral • Partial bilateral • Full/partial	3 25 10	6 23 6	0.37
Any upgrading, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	7 (12.1) 7 (12.1) NA NA	14 (26.9) 2 (3.8) 4 (7.6) 8 (15.3)	0.052 0.29 NA NA
Upgrading with risk group change, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	7 (12.1) 7 (12.1) NA NA	12 (23.1) 2 (3.8) 6 (11.5) 4 (7.6)	0.12 0.14 NA NA
Upgrading without risk group change, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	0 (0) 0 (0) NA NA	2 (3.8) 0 (0) 1 (1.9) 1 (1.9)	0.074 1 NA NA
Any downgrading, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	7 (12.1) 7 (12.1) NA NA	7 (13.4) 3 (5.7) 2 (3.8) 2 (3.8)	0.84 0.29 NA NA
Downgrading with risk group change, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	6 (10.3) 6 (10.3) NA NA	7 (13.4) 3 (5.7) 2 (3.8) 2 (3.8)	0.65 0.42 NA NA
Downgrading without risk group change, N. (%)			
Overall Respect to FB only Respect to FB and SB Respect to SB only	0 (0) 1 (1.7) NA NA	0 (0) 0 (0) 0 (0) 0 (0)	1 0.34 NA NA
Index lesion at RARP			
Homolateral to MRI index lesion Contralateral to MRI index lesion but homolateral to SB index lesion	51 (87.9) NA	46 (88.5) 4 (7.6)	0.98 NA
Contralateral to MRI and SB index lesion	NA	2 (3.8)	NA
Positive surgical margins; N. (%)	19 (32.8)	19 (36.5)	0.67

FB: fusion biopsy; SB: standard biopsy; MRI: multiparametric resonance imaging.

Table III. Analysis of Arm B patients with positive SB only.

	PCa at SB only (20 pts)	csPCa at SB only (14 pts)
Age, years; mean (IQR)	67.7 (63.0-75.5)	68.0 (64.0-75.0)
PSA, ng/dL; mean (IQR)	5.9 (3.7-7.3)	6.4 (3.8-7.5)
PSA density, ng/ml^2; (IQR)	0.12 (0.09-0.14)	0.12 (0.10-0.14)
Suspicious DRE, number (%)	6 (30)	3 (21)
Prostate volume, CC; mean (IQR)	51.4 (36.7-59.3)	55.6 (37.0-71.0)
Lesion volume, CC; mean (IQR)	0.34 (0.14-0.30)	0.32 (0.14-0.28)
PiRads score, number (%)		
3 ≥4	6 (30) 14 (70)	4 (29) 10 (71)
Number of positive SB cores, mean (IQR)		
Homolateral to MRI index lesion Controlateral to MRI index lesion	2.3 (1.5-2.5) 2.0 (1.0-3.0)	2.5 (1.0-4.0) 2.3 (1.0-5.0)
Concordance between SB positive sampling and MRI index lesion, number (%)	16/20 (80)	11/14 (79)
Concordance between SB positive sampling and RARP index lesion, number (%)	6/8 (75)	6/8 (75)

PCa: prostate cancer; csPCa: clinical significant prostate cancer; FB: fusion biopsy; SB: standard biopsy; DR: detection rate)

Table IV. Summary of different biopsy modalities performances.

	Arm A (FB) (201 pts)	Arm B (FB+SB) (193 pts)	DELTA DR (Arm B – Arm A)
Overall PCa detection rate, number (%)	FB 128 (63.7)	FB+Bilateral SB 137 (71.0)	+7.3%
	FB 128 (63.7)	FB+Homolateral SB 129 (66.8)	+3.1%
csPCa detection rate, number (%)	FB 121 (60.2)	FB+Bilateral SB 117 (60.6)	+0.4%
	FB 121 (60.2)	FB+Homolateral SB 115 (59.6%)	-0.6%

PCa: prostate cancer; csPCa: clinical significant prostate cancer; FB: fusion biopsy; SB: standard biopsy; DR: detection rate.

Figure 1.
A) LogPCA model computed on the overall cohort showed no graphical differences between the arms, since the clusters of the two arms are overlapped; B) Pearson's correlation values and correlation funnel showed that all the correlation values turned to be between -0.5 and +0.5, thus indicating no significant relation between the two arms; C) LogPCA model computed on cohort of patients who underwent RARP, showed no discrepancies between the two arms; D) Pearson's correlation values with correlation funnel indicated similar surgical outcomes despite the different biopsy approach.