Oncological and Functional prognostic value of Unconventional Histology of Prostate Cancer in Localized disease treated with Robotic Radical Prostatectomy: An International Multi-Center 5-year Cohort Study

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Abstract

Background: The impact of Unconventional Histologies (UH) of Prostate Cancer (PCa), [Cribriform Patterns(CP), Ductal (DAC) and Intraductal (IDC) Carcinoma] as compared to Pure Adenocarcinoma (AC) on Oncological and Functional outcomes after Robot Assisted Radical Prostatectomy (RARP) and the prevalence of adjuvant Radiotherapy (RT) in this cohort are unclear.

Objective: To compare UH vs pure Adenocarcinoma (AC) on short-mid term Oncological and Functional results and rates of Adjuvant RT after RARP.

Design, Setting, and Participants: We retrospectively collected data from a multicentric, International large cohort of men with Localized PCa treated with RARP between 2016 and 2020.

Outcome Measurements and Statistical Analysis: The primary outcomes included Biochemical Recurrence (BCR)-free survival, erectile and continence function; while the secondary outcomes included the need for adjuvant RT. Kaplan-Meier curves and Cox regression analysis were performed.

Results and Limitations: Overall, 3935 patients were included. At a median follow up of 2.8 years, HU had higher rates of BCR [IDC (17%; p<0.001),AC (10.7%)], and Adjuvant RT [DAC (6.3%; p=0.003), IDC (11.2%; p<0.001), AC (4.5%)]. There was significantly poorer 5-year BCR-free survival for UH groups compared to pure AC [HR: DAC =1.67 (95% CI 1.16 – 2.40), p=0,005; IDC=5.22 (95% CI 3.41 – 8.01), p<0,001; CP= 3,45 (95% CI 2.29 – 5.20), p<0,001]. Logistic regression analysis of functional outcomes found that the risk of new-onset erectile dysfunction at 1 year, when compared to ISUP 1-3 adenocarcinoma, was doubled in UH (HR: 2.13 for DAC, p<0.001; HR 2.14 for IDC, p<0.001; HR 2.01 for CP, p=0.011). Moreover, CP significantly increased the risk of incontinence (OR 1.97, p<0.001), but not IDC or DAC. The study was limited by the lack of central histopathological revision and relatively short follow up.

Conclusions: In this large cohort**,** the presence of UH after RARP was associated with worse short-mid term oncological outcomes; IDC independently predicted higher rates of adjuvant RT. At 1-year follow up, patients with UH had three times higher risk of erectile dysfunction post RARP; CP was associated with two-fold higher incontinence rates.

Patient Summary: Patients with Prostate Cancer treated with robotic prostatectomy have worse results in terms of cancer control, erection and continence; there is also a higher chance to receive additional radiotherapy after surgery.

Keywords: Prostate Cancer; Cribiform Pattern Prostate Cancer; Intraductal Prostate Cancer, Ductal Prostate Cancer, Unusual Histologies

1.Introduction

Prostate Cancer (PCa) is the second most frequently diagnosed cancer in men worldwide [1], with a worldwide estimated number of 1414,259 new cases in 2020 [2]; it is a urological malignancy that has growing economical burden, especially in elderly population [3].

Acinar Adenocarcinoma (AC) is the prevalent Histology. The Gleason grading system, and the International Society of Urological Pathology (ISUP) Grade Group derived from it [4], is one of the most important prognostic factors, widely used for driving disease management plans [5].In addition to Gleason score, according to a recent Systematic Review, the presence of Unconventional Histologies (UH), in particular Intraductal Carcinoma (IDC) , Cribriform Pattern (CP), and Ductal Carcinoma (DAC), may carry worse oncological prognosis than that of conventional and mucinous or PIN-like PCa. [6] While the histology results from that study [6] were retrieved both from prostate biopsy and Radical Prostatectomy, recent studies have suggested that Prostatectomy rather than biopsy should be the gold standard in determining Gleason scores and diagnosing IDC/ CP, in light of the limited concordance rates [7, 8]. Indeed, both the Genitourinary Pathology Society (GUPS) and ISUP, recommend reporting the percentage of Gleason pattern 4 and the presence of CP (present in 1% of PCa), which is associated with increased biochemical recurrence (BCR) (HR 2.1) and cancer-specific mortality (HR 3.3) [9,10,11,12]. According to the available literature, DAC is the second most frequent unconventional histology and its presence was suggested to predict PSA recurrence [13] and associated with worse overall mortality and metastasis-free survival [14]; IDC was found to be more prevalent in metastatic PCa [15]. However, most of these data were collected in the early 2000s, the specifications about the surgical approaches used were lacking and the impact of UH on functional outcomes was unexplained.

Radical Prostatectomy (RP) has been one of the curative treatment options for localized PCa [5]; in the last 10 years, the surgical techniques for RP evolved from open to minimally invasive surgery: Robot-Assisted laparoscopic Radical Prostatectomy (RARP) became an established and safe surgical modality [16]. To date, there remain unanswered questions regarding the impact of UH in PCa on functional and oncological results after RARP.

Moreover, although current guidelines support the use of Adjuvant RT in pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins [5], there has been no clear recommendation on the need for adjuvant treatment for PCa patients with the above UH.

We aim to provide contemporary updates on the prognostic value of UH in PCa at final histopatology assessment both in oncological and functional outcomes within a multicentric large cohort

of patients treated with RARP. Secondarily, we aim to evaluate the potential differences in the rates of adjuvant RT after RARP among the various histology groups.

2. Methods

We retrospectively collected data from consecutive RARP performed from 2016 to 2020 among seven international high volume centers. Patients with prior PCa treatment and mixed histology subtypes were excluded. Preoperative metastatic screening with imaging was employed according in patients with EAU intermediated and high risk cancer according to EAU risk group. The need for lymph node dissection was taken according to risk nomograms.

Baseline demographics (i.e. age, PSA and prostate size) and pathological (i.e. histological patterns, tumor and nodal staging), were retrieved and analysed.

2.1 Outcomes of interest

The Oncological Outcomes of interest included: BCR, as defined, according to EAU Guidelines, as two consecutive rising PSA values >0.2 ng/ml [5]; Adjuvant RT, as defined as RT planned after RARP based on clinicopathological risk factors before the occurrence of BCR and performed within 4-22 weeks from RARP [17] regardless of the dose and its fractionation. Other Oncological outcomes, such as rates of positive surgical margin, Lymph node involvement, nodal and Distant metastases were additionally collected.

The Functional Outcomes of interest included: Continence, as defined as no more than one protective pad per day [18]; Potency , as defined as the ability to obtain an erection rigid enough for intercourse with or without the use of a PDE-5I at least half of the time [19];

2.2 Pathological evaluation and Study Groups

In each centre, the RARP specimens had been entirely sampled and embedded for diagnostic purposes as previously described [20] and assessed by dedicated uropathologists. Histological types, Gleason score, ISUP Group according to the 2014 ISUP/2016 WHO guidelines (Epstein 2016), presence of IDC, pT and pN stage according to the American Joint Committee on Cancer TNM 8th edition (AJCC) and surgical margin status were retrospectively retrieved by the reports of RARP specimens [21, 22].

Four groups of malignant prostatic lesions were considered: Pure AC (Group 1), AC with CP (Group 2), DAC (Group 3) and IDC (Group 4) (see Figure 1). The latter three groups consisted of malignant prostatic lesions with CP and were defined according to the WHO classification [23]. In brief, DAC is composed of papillary structures and /or cribriform glands lined by tall columnar pseudostratified cells and basal cells are absent. We considered both the pure form and admixed with acinar AC. IDC was defined as a complex cribriform growth and lumen expansile proliferation of malignant epithelial cells within native ducts and acini with intact basal cells. In this study, IDC cases associated with invasive acinar AC were

considered. CP, one of the four patterns of Gleason grade 4 of AC, was defined as confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina without intervening stroma or mucin separating glandular structures [9].

2.3 Statistical Analyses

Statistical comparison was made among the four Groups. Continuous variables were presented as median (IQR) and compared using Mann-Whitney U test. Categorical variables were presented as count (percentage) and compared using Chi-squared test or Fisher's exact test. Kaplan-Meier curves were used in outcome comparison, and Cox regression analysis was performed to adjust for potential confounding factors. SPSS was used for the statistical analyses. Taking that for granted DAC without an AC component is, by definition, assigned a Gleason score of 4 + 4 = 8 (ISUP Grade 4), as its clinical behavior has been shown to be similar to that of AC of this grade [24], we compared AC ISUP 1-3 vs ISUP 4 vs ISUP 5 vs UH.

3. Results

From a total of 5005 Patients, 1070 cases had mixed or unreported histology and were therefor excluded; a total of 3935 PCa cases were suitable for analysis. Among them, 3126 had pure AC (Group 1); 174 had AC with CP (Group 2), 447 had DAC (Group 3), 188 had IDC (Group 4) (see Figure 1).

3.1 Baseline Characteristics

Baseline patient's and disease characteristics are listed in Table 1. Overall, median age was 65 (60-70), the median PSA was 6.8ng/mL (5-10), and the median prostate size was 38cc (28-53). Regarding ISUP grade group, overall there was a prevalence of ISUP 1-3[1(22.6%), 2(38.0%), 3(17.6%), 4(7.4%), 5(5.6%)], while in 8.7% the ISUP grades were not reported.

The IDC and CP had similar median PSA and prostate sizes, compared to AC. The DAC group had a significantly lower median PSA (6.1ng/mL) than AC (6.9ng/mL), but similar median age and prostate sizes, Compared to AC, the ISUP grades for each of the UH were significantly higher ($p<0.001$). AC had 77.6% IUSP 1-3 disease, whereas the majority of UH (DAC 66.7%, IDC 74.5% and CC 81.6%) were ISUP 2-3.

3.2 Oncological Outcomes

At a median follow of 2.8 years, BCR was more commonly observed in 17% of IDC ($p<0.001$) in comparison with AC (10.7%); there were significantly higher rates of positive surgical margin in any UH Group [DAC 33.6%, $p=0.04$; IDC 42.6% and CC 43.1%, $p<0.001$] than in AC (27.3%). Lymph node involvement was more common in DAC (6.9%, $p<0.001$) and IDC (8%, $p<0.001$) than in AC (0.5%). More nodal recurrence was observed in DAC (1.6%, $p<0.001$) and CC (2.9%, $p=0.049$), than in AC (0.4%).

Distant metastases occurred more frequently in DAC (1.1%, p=0.002) and IDC (3.7%, p=0.002), than in AC (0.9%) [Table 2].

In Figure 1, the Kaplan-Meier curve revealed significant differences in the BCR-free survival in 5 years. Compared to ISUP 1-3, IDC had the worst BCR rates, followed by CP, ISUP 5 AC, DAC and ISUP 4 AC (p<0.001).

Upon univariate Cox regression analysis, each UH group was associated with significantly poorer 5-year BCR-free survival when compared to pure AC, (hazard ratios: 1.67 for DAC, 5.22 for IDC, and 3.45 for CC) [Table 3].

Upon multivariable Cox regression analysis with reference to ISUP 1-3 disease [Table 5], the significant predictors for BCR at 5 years included DAC (HR 3.15, p<0.001), IDC (HR 5.63, p<0.01), CP (HR 3.94, p<0.001), presenting PSA (HR 1.63, p=0.001), pT3b stage (HR 2.19, p=0.007). Meanwhile, ISUP 4 (HR 2.07, p=0.096), ISUP 5 (HR 3.15, p=0.101), age (HR 1.0, p=0.98), pT3a (HR 2.19, p=0.097), positive margin (HR 1.47, p=0.069) and positive node (HR 0.88, p=0.724) were not significant predictors for BCR.

3.3 Functional Outcomes

There was 2-3 fold higher risk of de novo erectile dysfunction at one year postoperatively for each UH subgroup than AC. Moreover, CP was associated with two-fold higher incontinence rates than AC in one year postoperatively [Table 7]. Upon multivariable Cox regression analysis with reference to ISUP 1-3 disease [Table 8], the presence of any of DAC (HR 2.13, p<0.001), IDC (HR 2.14, p<0.001) and CP (HR 2.01, p=0.011) doubled the risk of 1-year erectile dysfunction. The other significant predictors for erectile dysfunction were pT3a (HR 1.67, p<0.001) and pT3b (HR 1.69, p=0.003). ISUP 4 and 5, as well as positive margin were not significant predictors. Contrarily, nerve-sparing techniques (HR 0.75, p=0.005) and lymph node dissection (HR 0.58, p<0.001) predicted less erectile dysfunction.

3.4 Adjuvant RT rates

The use of adjuvant RT in all the participating centres was in accordance with EAU guidelines [5]. Adjuvant RT was more prevalently adopted in DAC (6.3%, p=0.003) and IDC (11.2%, p<0.001) than in AC (4.5%).

Upon logistic regression analysis for predictors of adjuvant RT, as compared to ISUP 1-3, the IDC type was found to associate with a higher likelihood of adjuvant RT (OR 27.3 [CI 6.79-109.7]; p<0.001 [Table 6]. DAC also predicted increased risk of adjuvant RT (OR 3.27 [1.25-8.55]; p=0.015). Nodal metastasis (OR 9.09 [CI 2.49-33.24]; p<0.001), and seminal vesicle invasion (OR 8.13 [CI 3.51-18.8]; p<0.001) were the other significant predictors. CP (OR 4.2 [CI 0.08-2.27]; p=0.313), ISUP 4 and 5, positive margin and PSA were not significant predictors for adjuvant RT.

In addition, adjuvant RT was more likely to be required in DAC (HR 1.9) and IDC (HR 3.84) than in AC, by univariate logistic regression analysis [Table 4].

4.Discussion

In this large multicentric cohort of men with localized PCa treated with RARP, the presence of UH (namely DAC, CP and IDC) was significantly associated with 3-5 times increased 5-year BCR risk compared to ISUP 1-3 pure AC [Table 5]. Moreover, the risk of adjuvant RT was increased by 3 times for DAC and 27 times for IDC, from logistic regression analyses in comparison with ISUP 1-3. In terms of functional outcomes, the risk of new-onset erectile dysfunction at 1 year postoperatively was consistently increased by 2 times in all UH subtype [Table 8], compared to that of ISUP 1-3 adenocarcinoma; CP further showed increased risk of incontinence.

To the best of our knowledge, this is the first multi-centre large study to evaluate the impact of UH of PCa in the functional and oncological outcomes after RARP and the rates of adjuvant RT.

UH are not as rare as the conventional perception, accurate pathological description is mandatory. A recent systematic review by Porter et al highlighted that the incidence of IDC could reach 36.7% in high-risk disease and 56% in metastatic or recurrent disease [15]. A review by Montironi et al also showed that IDC was strongly associated with aggressive PCa with high Gleason score, large tumor volume and usually posed deleterious impact on prognosis [25]. The authors suggested that pathologists should report IDC in prostate specimens, especially in prostate biopsy, because it is critical for patient management.

Ericson et al reported that prostate biopsy had sensitivity of 56.5% and specificity of 87.2% for detection of cribriform and/or intraductal carcinoma post radical prostatectomy, and that MRI-USG fusion prostate biopsy did not improve the detection of UH. [26] Although biopsy cannot confidently rule out UH, patients with biopsy-proven UH histology (especially IDC) should be informed of the increased risk of BCR and adjuvant RT, and advised to receive active treatment. In addition, post RALP diagnosis of UH should trigger discussion about the option of adjuvant RT, or at least more strict follow-up in order to pick up the relatively early BCR as shown in our study.

The adverse oncological behaviours of these UH are by no means isolated reports, and therefore warrant more attention by modern practising urologists. Kweldam et al showed that among the different Gleason 4 grade patterns, CP was independently associated with inferior metastasis-free survival and disease-specific mortality rates in patients with Gleason 7 PCa following RP[10]. In the 2005-2018 cohort by Ranasinghe et al, DAC treated by either RP or RT was associated with worse 5-year metastasis-free and overall survival rates, when compared to high-risk PCa [14]. On top of the systematic review Russo et al. showing inferior oncological outcomes for CP[27], a recent study found that CP had typically worse response to androgen blockade, suggesting that this UH could contribute to hormonal deprivation resistance

[28]. Besides, CP was also found to be associate with an increased lymph node positive status at prostatectomy [29]. In our analysis, CP was the strongest predictor of BCR at Cox regression analysis, with a risk of 5.5 folds. This reiterates the importance of reporting PCa UH on specimens.

Several unanswered questions remain in the management of UH PCa histology. For instance, whether there are differences in the response to RT (especially for IDC), multimodal therapy, androgen deprivation therapy in the (neo-)adjuvant and palliative settings, novel hormonal agents or chemotherapy, and what should be the optimal follow-up protocols. Moreover, genomic alterations have been linked to the development of intraductal and cribriform subtypes of PCa by Chua et al. [30] Future trials would therefore be needed to elucidate the role of genetics and optimal management for patients with these PCa UH.

The functional outcomes after RARP are clearly multifactorial and affected by intraoperative (e.g. nerve-sparing, urethral length and bladder neck preservation and reconstruction strategies) and postoperative factors (e.g. rehabilitation programs). Nevertheless, this phenomenon is thought-provoking, and can be partly explained by the higher RT rates for UH in our study. Further studies are warranted to elucidate the association between UH and worse functional outcomes.

There are several limitations to our study: 1) The retrospective nature of the data collected, 2) lack of central revision of histological specimen, 3) lack of preoperative imaging details and data of patients treated primarily with RT, 4) omission of rarer UH such as mucinous/neuroendocrine disease, 5) unstandardized follow-up protocols among the participating centres and lastly 6) the relatively short follow up (2.8 years) of our case series. Further prospective studies are needed to confirm our findings.

5. Conclusion

When prostate cancer patients were treated with RARP, the presence UH (CC, DAC and IDC) was associated with increased early BCR than ISUP 1-3 AC. Moreover, DAC and IDC predicted higher rates of adjuvant RT. In terms of functional results, the presence of any of the investigated UH predicted two times higher risk of erectile dysfunction in one year postoperatively, with CP associated with an additional higher risk of incontinence. Patients diagnosed with these UH should be well counselled about their risk profiles, followed up stringently, and educated about the higher likelihood of multimodality treatment.

Author contributions: Prof. Jeremy Teoh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: JYCT, DL, DC

Acquisition of data: All

Analysis and interpretation of data: DL, RN

Drafting of the manuscript: DL, RN

Critical revision of the manuscript for important intellectual content: DC, RM

Statistical analysis: JYCT, DL, RN

Supervision: DC, JYCT

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Graphs and Tables

Figure 1 – Group definition and number of patients for each Group. Four Groups were compared in the Analysis: Group 1 (Pure Adenocarcinoma), Group 2 (Adenocarcinoma with Cribiform Pattern), Group 3 (Ductal Carcinoma) and Group 4 (Intraductal Carcinoma).

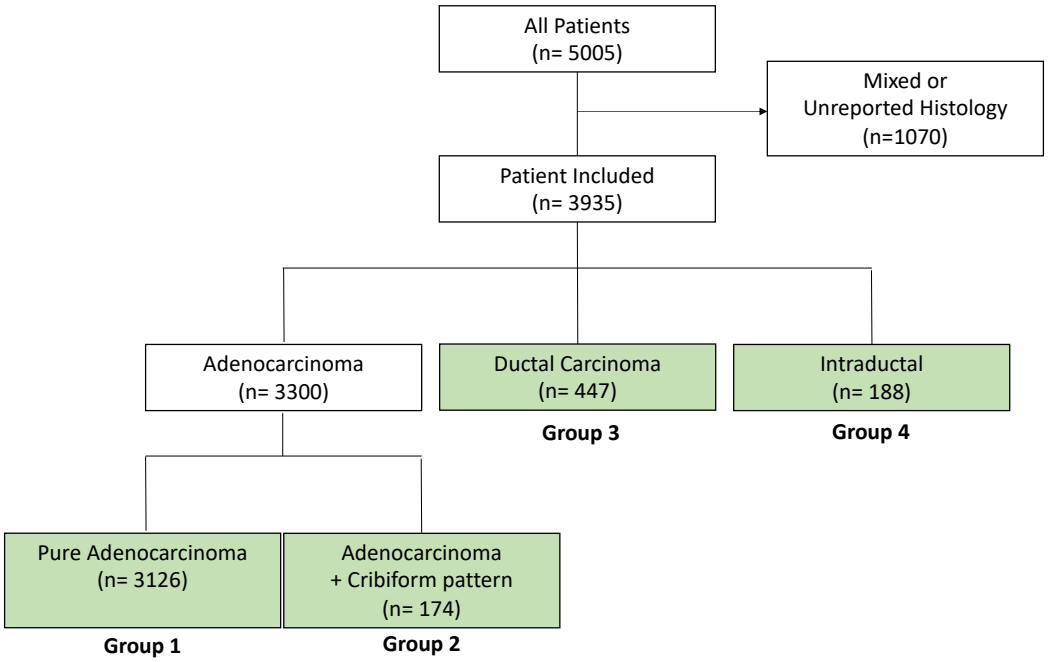

Table 1 Baseline Patient's and Disease's characteristics.

	Pure Adenocarcinoma (N = 3126)	Ductal (N = 447)	P	Intraductal (N = 188)	P	Cribriform (N = 174)	P	Total (N = 3935)
Age	65 (60 – 70)	65 (60 – 70)	0.683	67 (61 – 71)	0.043	67 (62 – 70)	0.015	65 (60 – 70)
PSA	6.9 (5.0 – 10.0)	6.1 (4.3 – 8.5)	<0.001	7.2 (5.0 – 12.1)	0.365	6.5 (5.1 – 9.0)	0.243	6.8 (5.0 – 10.0)
Prostate size	39 (28 – 54)	37 (30 – 52)	0.733	41 (32 – 59)	0.054	33 (25 – 50)	0.001	38 (28 – 53)
Prostatectomy			<0.001		<0.001		<0.001	
ISUP								
1	815 (26.1)	73 (16.3)		1 (0.5)		1 (0.6)		890 (22.6)
2	1123 (35.9)	213 (47.7)		63 (33.5)		98 (56.3)		1497 (38.0)
3	488 (15.6)	85 (19.0)		77 (41.0)		44 (25.3)		694 (17.6)
4	240 (7.7)	21 (4.7)		14 (7.4)		17 (9.8)		292 (7.4)
5	164 (5.2)	21 (4.7)		22 (11.7)		14 (8.0)		221 (5.6)
Missing	296 (9.5)	34 (7.6)		11 (5.9)		0 (0)		341 (8.7)

Table 2 Oncological Outcomes

	Pure Adenocarcinoma (N = 3126)	Ductal (N = 447)	P	Intraductal (N = 188)	P	Cribriform (N = 174)	P	Total (N = 3935)
Surgical margin			0.039		<0.001		<0.001	
Positive	854 (27.3)	150 (33.6)		80 (42.6)		75 (43.1)		1159 (29.5)
Negative	2009 (64.3)	282 (63.1)		95 (50.5)		96 (55.2)		2482 (63.1)
Missing	263 (8.4)	15 (3.4)		13 (6.9)		3 (1.7)		294 (7.5)
Lymph node involvement			<0.001		<0.001		0.273	
Yes	16 (0.5)	31 (6.9)		15 (8.0)		4 (2.3)		66 (1.7)
No	781 (25.0)	236 (52.8)		51 (27.1)		99 (56.9)		1167 (29.7)
Missing	2329 (74.5)	180 (40.3)		122 (64.9)		71 (40.8)		2702 (68.7)
Adjuvant RT			0.003		<0.001		0.902	
Yes	141 (4.5)	28 (6.3)		21 (11.2)		9 (5.2)		199 (5.1)
No	2400 (76.8)	251 (56.2)		93 (49.5)		160 (92.0)		2904 (73.8)
Missing	585 (18.7)	168 (37.6)		74 (39.4)		5 (2.9)		832 (21.1)
Salvage RT			<0.001		0.002		0.214	
Yes	239 (7.6)	23 (5.1)		16 (8.5)		21 (12.1)		299 (7.6)
No	2200 (70.4)	36 (8.1)		61 (32.4)		143 (82.2)		2440 (62.0)
Missing	687 (22.0)	388 (86.8)		111 (59.0)		10 (5.7)		1196 (30.4)

Biochemical recurrence			0.671		<0.001		0.078	
Yes	334 (10.7)	48 (10.7)		32 (17.0)		30 (17.2)		444 (11.3)
No	2203 (70.5)	295 (66.0)		85 (45.2)		137 (78.7)		2720 (69.1)
Missing	589 (18.8)	104 (23.3)		71 (37.8)		7 (4.0)		771 (19.6)
Nodal recurrence			<0.001		0.325		0.049	
Yes	11 (0.4)	7 (1.6)		1 (0.5)		5 (2.9)		24 (0.6)
No	1045 (33.4)	24 (5.4)		34 (18.1)		156 (89.7)		1259 (32.0)
Missing	2070 (66.2)	416 (93.1)		153 (81.4)		13 (7.5)		2652 (67.4)
Metastasis			0.002		0.002		1	
Yes	29 (0.9)	5 (1.1)		7 (3.7)		4 (2.3)		45 (1.1)
No	1181 (37.8)	28 (6.3)		57 (30.3)		160 (92.0)		1426 (36.2)
Missing	1916 (61.3)	414 (92.6)		124 (66.0)		10 (5.7)		2464 (62.6)
Status			0.007		1		1	
Alive	2592 (82.9)	445 (99.6)		139 (73.9)		166 (95.4)		3342 (84.9)
Dead	43 (1.4)	0 (0)		2 (1.1)		2 (1.1)		47 (1.2)
Unknown	491 (15.7)	2 (0.4)		47 (25.0)		6 (3.4)		546 (13.9)
Median follow-up	1039 (553 – 1674)	1223 (803 – 1647)	<0.001	888 (357 – 1212)	<0.001	867 (480 – 1190)	<0.001	1045 (573 – 1616)

Graph 1

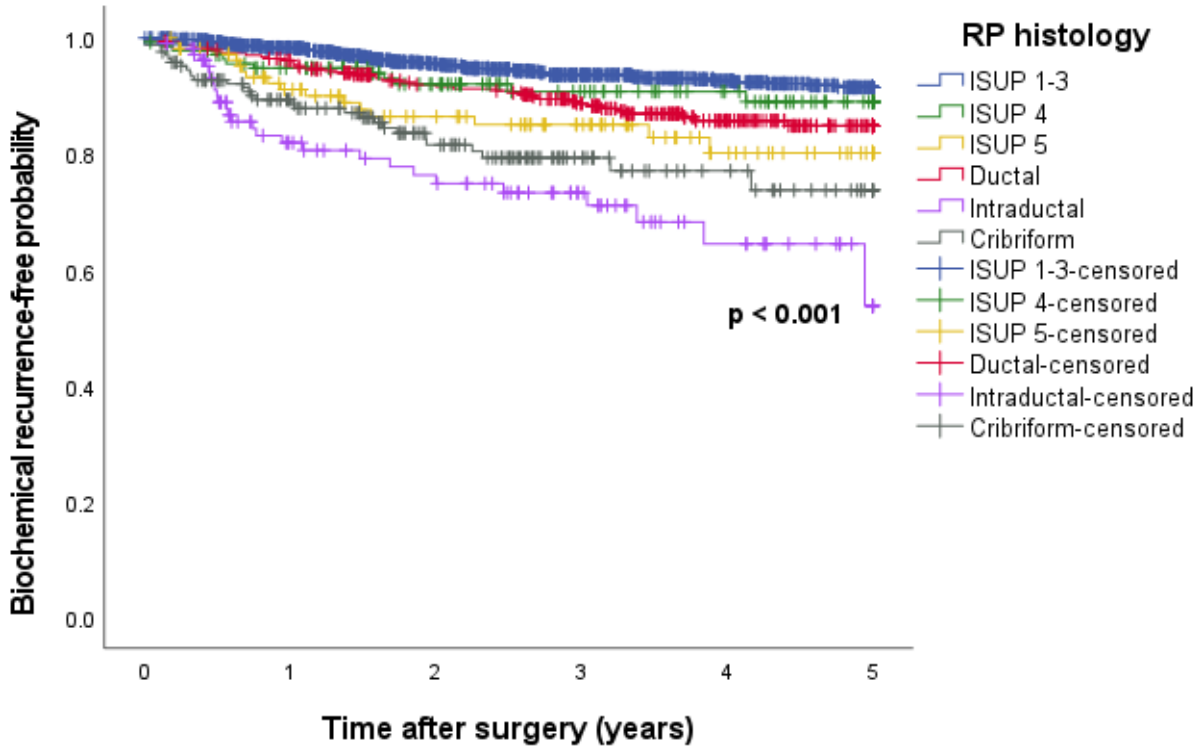

Table 3. Univariate Cox regression analysis for 5-year biochemical recurrence-free survival (pure adenocarcinoma as reference group)

Risk factor	Hazard ratio (95% CI)	P-value
Ductal vs pure adenocarcinoma	1.67 (1.16 – 2.40)	0.005
Intraductal vs pure adenocarcinoma	5.22 (3.41 – 8.01)	<0.001
Cribriform vs pure adenocarcinoma	3.45 (2.29 – 5.20)	<0.001

Table 4. Univariate logistic regression analysis for adjuvant RT (pure adenocarcinoma as reference group)

Risk factor	Hazard ratio (95% CI)	P-value
Ductal vs pure adenocarcinoma	1.90 (1.24 – 2.91)	0.003
Intraductal vs pure adenocarcinoma	3.84 (2.32 – 6.36)	<0.001
Cribriform vs pure adenocarcinoma	0.96 (0.48 – 1.91)	0.902

Table 5. Multivariable Cox regression analysis for 5-year biochemical recurrence-free survival (ISUP 1-3 as reference)

Risk factor	Hazard ratio (95% CI)	P-value
RP histology		
Adenocarcinoma ISUP 1-3	Reference	-
Adenocarcinoma ISUP 4	2.07 (0.88 – 4.90)	0.096
Adenocarcinoma ISUP 5	2.02 (0.87 – 4.68)	0.101
Ductal	3.15 (1.72 – 5.78)	<0.001
Intraductal	5.63 (2.74 – 11.58)	<0.001
Cribriform	3.94 (2.14 – 7.25)	<0.001
Age	1.00 (0.97 – 1.03)	0.985
PSA*	1.63 (1.21 – 2.19)	0.001
Nerve-sparing	0.63 (0.40 – 0.99)	0.047
Pathological T stage		
pT2	Reference	-
pT3a	1.56 (0.92 – 2.64)	0.097
pT3b	2.19 (1.24 – 3.85)	0.007
Positive margin	1.47 (0.97 – 2.24)	0.069
Positive node	0.88 (0.42 – 1.83)	0.724

* PSA was log-transformed

Table 6 Logistic regression analysis for adjuvant RT (ISUP 1-3 as reference)

Risk factor	Odds ratio (95% CI)	P-value
RP histology		
Adenocarcinoma ISUP 1-3	Reference	-
Adenocarcinoma ISUP 4	3.41 (0.96 – 12.09)	0.058
Adenocarcinoma ISUP 5	0.70 (0.12 – 3.94)	0.686
Ductal	3.27 (1.25 – 8.55)	0.015
Intraductal	27.31 (6.79 – 109.74)	<0.001
Cribriform	0.42 (0.08 – 2.27)	0.313
PSA*	1.60 (0.91 – 2.80)	0.101
Positive margin	1.08 (0.48 – 2.41)	0.856
Seminal vesicle invasion	8.13 (3.51 – 18.82)	<0.001
Positive node	9.09 (2.49 – 33.24)	<0.001

* PSA was log-transformed

Logistic regression analysis for adjuvant RT (ISUP 1-3 as reference)

Risk factor	Odds ratio (95% CI)	P-value
RP histology		
Adenocarcinoma ISUP 1-3	Reference	-
Adenocarcinoma ISUP 4	3.41 (0.96 – 12.09)	0.058

Adenocarcinoma ISUP 5	0.70 (0.12 – 3.94)	0.686
Ductal	3.27 (1.25 – 8.55)	0.015
Intraductal	27.31 (6.79 – 109.74)	<0.001
Cribriform	0.42 (0.08 – 2.27)	0.313
PSA*	1.60 (0.91 – 2.80)	0.101
Positive margin	1.08 (0.48 – 2.41)	0.856
Seminal vesicle invasion	8.13 (3.51 – 18.82)	<0.001
Positive node	9.09 (2.49 – 33.24)	<0.001

* PSA was log-transformed

Table 7 Comparison of functional outcomes at 1 year postoperatively

	Odds Ratio (95% CI)	
	Incontinence	ED
Ductal vs adenocarcinoma	1.03 (0.77 – 1.39), p = 0.839	1.95 (1.58 – 2.42), p < 0.001
Intraductal vs adenocarcinoma	1.51 (0.92 – 2.50), p = 0.104	2.63 (1.85 – 3.73), p < 0.001
Cribriform vs adenocarcinoma	1.97 (1.33 – 2.92), p < 0.001	3.03 (1.82 – 5.05), p < 0.001

Table 8 Logistic regression analysis for 1-year erectile dysfunction (ISUP 1-3 as reference)

Risk factor	Hazard ratio (95% CI)	P-value
RP histology		
Adenocarcinoma ISUP 1-3	Reference	-
Adenocarcinoma ISUP 4	0.94 (0.67 – 1.31)	0.700
Adenocarcinoma ISUP 5	0.76 (0.50 – 1.16)	0.201
Ductal	2.13 (1.67 – 2.70)	<0.001
Intraductal	2.14 (1.45 – 3.17)	<0.001
Cribriform	2.01 (1.18 – 3.45)	0.011
Age	1.00 (0.98 – 1.01)	0.477
PSA*	1.14 (1.00 – 1.30)	0.057
Nerve-sparing	0.75 (0.62 – 0.92)	0.005
Lymph node dissection	0.58 (0.47 – 0.70)	<0.001
Pathological T stage		
pT2	Reference	-
pT3a	1.67 (1.38 – 2.02)	<0.001
pT3b	1.52 (1.15 – 2.00)	0.003

pT4	1.69 (0.15 – 19.02)	0.673
Positive margin	0.99 (0.82 – 1.19)	0.898

* PSA was log-transformed

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