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Annals of Gerontology and Geriatric Research

Research Article

Impact of Radical Prostatectomy Delay on Oncological Outcomes in 2287 Patients over an Eleven-Year Timespan

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Submitted: 15 September 2023

Accepted: 21 September 2023

Published: 22 September 2023

ISSN: 2378-9409

Keywords

- Radical Prostatectomy
- Biochemical Recurrence
- Upgrading
- Upstaging

Abstract

Introduction: The impact of lengthening the delay between diagnosis and radical prostatectomy (RP) on oncological outcomes is uncertain. This study aimed to assess the impact of surgical delay on oncologic outcomes such as pathologic upgrading, pT3 upstaging and risk of biochemical recurrence (BCR).

Methods: This study retrospectively analyzed all consecutive radical prostatectomies carried out in a single center from January 2012 to May 2023. A surgical delay cutoff of 3 months was chosen. The primary endpoint was the assessment of BCR through the validated CAPRA-S score. Secondary endpoints included pathologic analyses such as ISUP upgrading, pT3 upstaging, positive surgical margins and nodal status.

Results: A total of 2287 patients were included, 1479 of which had complete data on surgical delays. Median age and PSA at diagnosis were 65.0 years (IQR [60.0; 69.0]) and 7.7 ng/ml (IQR [5.8; 10.2]) respectively. Median time between prostate biopsy and surgery was 3.0 months [3.0; 4.0]. Surgical delay over three months was found to be significantly associated with ISUP upgrading: from ISUP1 to ISUP2 in 4% vs 7% (p=0.042) and from ISUP2 to ISUP3 in 7% vs 13% (p=0.011), but not with upstaging to pT3, nor to positive surgical margins. The risk of biochemical recurrence was not higher in patients delayed over three months: CAPRA-S score 4.0 [3.0; 6.0] vs 4.0 [3.0; 6.0] (p=0.738).

Conclusion: While surgical delay could lead to higher ISUP upgrading, no negative impact on oncological outcomes such as pathologic locally advanced disease and risk of biochemical recurrence has been shown.

INTRODUCTION

While active surveillance is a standard in the low risk prostate cancer (PCa) population and its indication extends to ISUP2 cancer with certain restrictions [1], radical prostatectomy for localized prostate cancer has shown to reduce the risk of local and distant progression by twofold [2].

The restrictions recommended for intermediate-risk cancers are related to the controversy surrounding the time taken to treat these cancers. More generally, the question of the maximum time that can be allowed between the diagnosis of cancer and its radical treatment without having a negative impact on the prognosis of patients remains controversial [3]. While some studies suggest an unfavorable impact on biochemical recurrence (BCR) by delaying more than 6 to 9 months [4,5], a recent larger study by Diamand et al. found no difference on the rate of BCR with a delay of 3 months or higher in 926 intermediate and high-risk PCa [6]. Surgical delay has been proven not to influence metastasis-free survival [7] in intermediate to very-high risk patients. Similarly, pathological outcomes seem to vary according to surgical delay: upstaging with extra capsular extension (ECE) on final pathology was higher in patients delayed by more than 3 months [8] or older than 70 years [9]. Gleason score or ISUP since 2014 is one of the main predictors of the risk of risk of BCR after prostatectomy [10], yet we know that it is only poorly assessed by analysis of prostate biopsies. As up to a third of these patients are upgraded on the postoperative pathology [11].

The assumption is made that these heterogeneous results are due in part to a lack of standardized delay cutoff. Like other investigators, we found that a delay ≥3 months seemed to increased the risk of BCR [12], thus aim of this study was to confirm the prognostic value of this delay. Here we report oncological outcomes such as metastasis free and overall survival through the post-biopsy USCF-CAPRA score [13] and BCR free survival through post-surgery CAPRA-S scores [14].

MATERIAL AND METHODS

This study retrospectively analyzed all consecutive radical prostatectomies carried out in a single center from January 2012 to May 2023. Clinical, biological and histological data were gathered. PSA was collected using the last known PSA before biopsies, then by systematic PSA measurement the day

before surgery and prospectively after. All patients underwent systematic prostate biopsies (12 samples divided into 6 quadrants: base, median and apex on each side). All patients who had undergone multipara metric prostatic MRI prior to biopsy. For those who had a PIRADS >3 target lesion on MRI, additional targeted biopsies were performed using an ultrasound image fusion ultrasound-MRI image fusion guidance system (Urostation® system, Koelis, Grenoble, France). All patients underwent robotic-assisted radical prostatectomy. In accordance with the guidelines, extensive bilateral pelvic lymph node dissection was performed, except for patients with a cT2 stage and an ISUP 1 histological score on biopsies [15]. These were considered as pN0 for the calculation of the CAPRA-S score. All prostate biopsies and prostatectomy specimens were reviewed by 3 experienced pathologists. For all patients, the post-biopsy USCF-CAPRA score [13] and the post-surgery CAPRA-S score [14] were calculated.

RESULTS

Overall, 2310 patients were included in the primary analysis. Population characteristics of the overall cohort are presented in Table 1. Median time between prostate biopsy and surgery was 3.0 months [2.0; 4.0], the distribution of this delay is shown in Figure 1. Median preoperative PSA was 7.7 ng/ml [5.8; 10.2] with a PSA density of 0.17 ng/ml/g [0.12; 0.24]. Median BMI and Fat density were 26.0 kg/m^2 [24.2; 28.4] and 25.0 % [21.0; 29.0] respectively. Patients presented with clinical T1c, T2, and T3a in 58%, 41% and 1% of cases while T3b and T4 was present at diagnosis in only 5 patients (0%). ISUP 1 was present in 15% of cases while ISUP 2 and 3 represented 69% of patients. When classifying in the D'Amico risk classification: 12% of patients were at low risk and 12% were at high risk.

Pathologic analysis showed pT3a and pT3b in 36% and 10 % respectively, revealing a pT3 upstaging frequency from a lower clinical T stage of over 44%. ISUP upgrading at final pathology was present in 18% of patients, LNI in 6%.

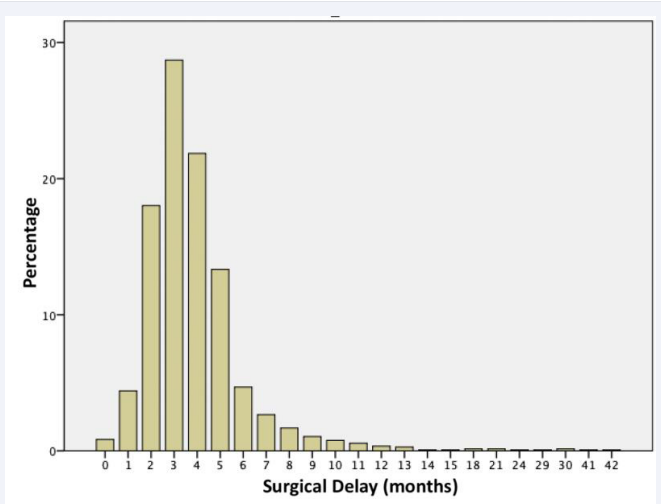

Figure 1 Surgical delay.

Table 1: IQR interquartile range, PSA prostate-specific antigen, PR prostatectomy

Population characteristics	Total (n=2287)
Age, years [IQR]	65.0 [60.0 ; 69.0]
Diabetes, n (%)	223 (10)
Cardiovascular disease, n (%)	239 (10)
BMI, kg/m2 [IQR]	26.0 [24.2 ; 28.4]
Fat density, % [IQR]	25.0 [21.0 ; 29.0]
PSA, ng/ml [IQR]	7.7 [5.8 ; 10.2]
PSA Density (ng/ml/g) [IQR]	0.17 [0.12 ; 0.24]
cT, n (%) (8% missing data) 1c 2 3a 3b 4	 1215 (58) 8 (41) 20 (1) 5 (0) 0 (0)
ISUP grade, n (%) 1 2 3 4 5	 333 (15) 1293 (57) 504 (22) 126 (4) 140 (4)
Damico risk classification, n (%) Low Intermediate low Intermediate High High	 279 (12) 1237 (54) 493 (22) 273 (12)
Lymphadenectomy, n (%)	1371 (59)
pT, n (%) 2 3a 3b 4	 1242 (54) 808 (36) 219 (10) 2 (0)
T Upstaging (cT1c/2 to pT3), n (%)	1005 (44)
Lymph node invasion, n (%)	130 (6)
Positive margins, n (%)	798 (35)
ISUP Upgrade, n (%)	406 (18)
Time to PR (months) [IQR]	3.0 [2.0 ; 4.0]
UCSF-CAPRA, n (%)(7% missing data) Total points [IQR] : Low risk (0-2), % Intermediate risk (3-5), % High risk (6-10), %	 4.0 [3.0 ; 6.0] 378 (16.5) 1193 (52) 530 (23)
CAPRA-S, n (%) (4% missing data) Total points [IQR] : Low risk (0-2), % Intermediate risk (3-5), % High risk (6-10), %	 4.0 [3.0 ; 6.0] 331 (15) 1314 (58) 629 (27)

Data on surgical delay was available for 1479 patients as shown in Table 2. Patients operated within 3 months had a higher rate of clinical stage 3a tumors and (1% vs 0% p=0.027) as well a higher proportion of ISUP 4 and 5 than those operated after 3 months of delay: 4% and 4% vs 2% and 1.3% (p=0.002). Surgical delay was found to be significantly associated with ISUP upgrading: from ISUP1 to ISUP2 in 4% vs 7% (p=0.042) and from ISUP2 to ISUP3 in 8% vs 13% (p=0.011). On pathologic analysis, surgical delay was not significantly associated with upstaging to pT3, nor to positive surgical margins. Lymphadenectomy was more frequent in patients operated within 3 months 65% vs 52% (p<0,001) with a similar rate of positive lymph nodes.

Surgical delay did not seem to impact the preoperative UCSF-CAPRA score 4.0 [3.0; 5.0] vs 4.0 [3.0; 6.0] (p=0.606) nor the post-operative CAPRA-S score 4.0 [3.0; 6.0] vs 4.0 [3.0; 6.0] (p=0.738), as well as subsequent risk categories.

Table 2: *Kruskal–Wallis tests for continuous and Chi-square tests for categorical data

Characteristics according to delay	Delay ≤3 months (n=761)	Delay >3 months (n=718)	p-value*
Age, years [IQR]	66.0 [61.0 ; 70.0]	66.0 [61.0 ; 70.0]	0.33
PSA, ng/ml [IQR]	7.5 [5.7 ; 10.0]	7.5 [5.7 ; 10.0]	0.77
Densité PSA, ng/ml/g [IQR]	0.17 [0.11 ; 0.25]	0.17 [0.11 ; 0.25]	0.90
Clinical T stage, n (%) 1c 2 3a 3b	 450 (59) 302 (40) 7 (1.0) 2 (0)	 444 (62) 274 (38) 0 (0) 0 (0)	0.027
ISUP grade, n (%) 1 2 3 4 5	 51 (7) 428 (59) 186 (26) 26 (4) 29 (4)	 62 (9) 409 (61) 163 (24) 14 (2) 9 (1)	0.002
DAMICO, n (%) faible Intermediaire faible Intermediaire élevé Élevé	 8 (1) 427 (57) 178 (23) 105 (14)	 6 (1) 441 (61) 156 (22) 59 (8)	0.374
Pathological T stage, n (%) 2 3a 3b 4	 425 (56) 270 (36) 62 (8) 1 (0)	 396 (55) 248 (35) 71 (10) 0	0.691
Positive margins, n (%)	252 (33)	261 (37)	0.346
Lymphadenectomy	492 (65)	370 (52)	<0.001
Positive lymph node, n (%)	44 (9)	33 (9)	0.887
ISUP upgrading, n (%) Any ISUP1 to ISUP2 ISUP1 to ISUP3 ISUP1 to ISUP≥4 ISUP2 to ISUP3 ISUP2 to ISUP≥4	 108 (15) 32 (4) 9 (1) 0 (0) 59 (8) 11 (2)	 165 (24) 50 (7) 13 (2) 1 (0) 92 (13) 13 (2)	 0.001 0.042 0.011
T Upstaging (cT1c/2 to pT3) , n (%)	324 (43)	320 (45)	0.463
CAPRA_UCSF, n (%) Total points [IQR] : Low risk (0-2) Intermediate risk (3-5) High risk (6-10)	 4.0 [3.0 ; 5.0] 106 (14) 451 (60) 201 (26)	 4.0 [3.0 ; 6.0] 127 (18) 420 (59) 170 (23)	 0.606 0.108
CAPRA_S, n (%) Total points [IQR] : Low risk (0-2) Intermediate risk (3-5) High risk (6-10)	 4.0 [3.0 ; 6.0] 113 (15) 435 (58) 209 (27)	 4.0 [3.0 ; 6.0] 103 (14) 411 (57) 202 (29)	 0.738 0.941

DISCUSSION

The results of this cohort of 1479 patients show that while surgical delay could lead to higher ISUP grade upgrade, no negative impact on oncological outcomes such as pathologic locally advanced disease and BCR has been shown.

These results are in line with most literature: upgrading of the ISUP grade on final pathology score may be linked to surgical delay but is not associated with BCR [16,17].

We chose the 3 month delay cutoff in accordance to previous studies [3,12], because the median delay of 3 months observed in the previous analysis made it possible to compare cohorts of similar size, and because this delay has shown a negative oncological impact in other urological cancers [18].

While similar results of 3 to 6 months delays on BCR have been found in other studies [6,7,19], this study benefits from a larger number of patients with a greater timespan. Furthermore, while targeted and systematic biopsy of the prostate has been associated with a reduction in the risk of overestimation and underestimation of the Gleason score, our cohort has the advantage of being contemporary with the use of these biopsy techniques. This reduces the bias associated with the poor quality of Gleason assessment using systematic biopsies alone [20].

We decided to include ISUP1 patients to analyze the rates of upgrading and upstaging in this low risk population: 15% of these patients are upstaged on pathologic analysis. This questions systematic active surveillance of these apparently nonthreatening low risk tumors [1] and some authors have suggested repeat biopsies before entering active surveillance [21]. Surveillance of intermediate risk patients impairs survival rate compared to low risk: OR, 0.43 [95% CI, 0.35–0.53] and metastases-free survival: OR, 0.46 [95% CI, 0.28–0.77] at 10 years [22]. Both intrinsic aggressiveness of the tumor and biopsy underassessment due to poor initial sampling or difficulty in interpretation by the pathologist could result in ISUP upgrading. The rates of upstaging and upgrading in this population are in line with a large population based study (n=16 818) [23].

One of the strengths of this study is comparativeness on clinical T stage and Damico risk stratification between the two subgroups. We also found that ISUP 4 and ISUP 5 patients tended to have prompter surgeries.

Several limitations exist in our study. We were unable to study the 12 months delay cutoff that has been proven to increase BCR and clinical recurrence [24] because it represented less than 5% of our population. The higher rate of ISUP 1 in the delayed surgery group may have increased the global ISUP upgrade rate, however, ISUP 2 distribution was similar between both groups and the upgrade rate from ISUP 2 is incontestable. Although its retrospective nature may induce several biases, we included all consecutive PR, with exhaustive reproducible data collection. While a prospective study would give a more rigorous definition of the maximum delay it is ethically questionable. Oncological outcomes were assessed theoretically through risk scores such as preoperative UCSF-CAPRA and postoperative CAPRA-S because many patients were lost during follow-up. These scores have been proven to be accurate predictors of the risk of BCR, metastasis and overall survival [13,14] and are used in our daily practice.

A prospective trial seems necessary to assess the rate of recurrence using the actual biological recurrence rate over several years.

CONCLUSION

In this single-center, longitudinal study including all patients who underwent radical prostatectomy over a 11-year period, we identified no statistically significant associations between surgical delay and adverse oncologic outcomes, such as

pathological locally advanced disease, positive surgical margins, or biochemical recurrence (BCR). The subgroup with a delay exceeding three months displayed a higher rate of ISUP score upgrade.

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