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ORIGINAL ARTICLE

## Migration in last decade to high-risk prostate cancer after radical prostatectomy

*Migration des stades après prostatectomie totale au cours des 10 dernières années vers un cancer de la prostate à haut risque*

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### KEYWORDS

Prostate cancer;  
Radical  
prostatectomy;  
Stage migration

### Summary

**Objective.** – There is controversy around prostate cancer (PCa) screening through the use of PSA, due to the risk of overtreatment. The current trend observed in various European and American studies is a decrease in the number of radical prostatectomy (RP) in low-risk PCa and an increase for intermediate or locally advanced diseases. The objective of this study was to observe the migration of the pathological stages from radical prostatectomy (RP) over 10 years in France through 2 French centers.

**Methods.** – It was a multicentric retrospective study, where all the RP realized in 2 French tertiary centers, in a laparoscopic or retroperitoneal approach for each of the years 2005, 2010 and 2015 were included. Preoperative data (age, PSA, clinical stage, number of positive biopsies, Gleason biopsy score) and postoperative data (pTNM, pathological Gleason score (pGS)) were analyzed and compared.

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**Results.** – In all, 1282 RP were realized (503 in 2005, 403 in 2010, 376 in 2015). Respectively between 2005, 2010, 2015 the average number of positive biopsy increased significantly from 2.30 vs. 2.88 vs. 5.3 ( $P=0.0001$ ). The distribution of D’Amico’s risk evolves with time: low-risk: 49.9 vs. 44.4 vs. 15.7% ( $P=0.0001$ ); intermediate risk: 40.95 vs. 43.92 vs. 64.1% ( $P=0.0001$ ) and high-risk: 9.15 vs. 11.66 vs. 20.2% ( $P=0.0001$ ) between 2005, 2010 and 2015 respectively. pGS evolved to higher score with SG < 7: 22.8 vs. 29.9 vs. 7.1% et SG  $\geq$  7: 77.2 vs. 70.1 vs. 92.9% ( $P=0.001$ ). Also, pTNM increased to non-organ-confined disease: pT2: 66.9 vs. 51.9 vs. 48.7%; pT3: 33.1 vs. 48.1 vs. 51.3% ( $P=0.0001$ ).

**Conclusion.** – This study showed a change in the management of PCa since new recommendations from medical authorities about PSA screening and evolving of conservative treatment. Number of RP increase for higher risk PCa. This change corresponds to better patient selection for RP: decrease for low-risk and increase for high-risk organ-confined disease.

**Level of evidence.** – 3.

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## MOTS CLÉS

Cancer de la prostate ;  
Prostatectomie ;  
Migration des stades

## Résumé

**Objectif.** – Il existe une controverse autour du dépistage du cancer de prostate (CaP) par l’utilisation du PSA, en raison du risque de surtraitement. La tendance actuellement observée dans différentes études Européennes et Américaines est une diminution du nombre de prostatectomie totale (PT) dans les CaP de bas risque et une augmentation pour les maladies de pronostique intermédiaire ou localement avancée. L’objectif de cette étude était d’observer la migration des stades pathologiques sur 10 ans des patients subissant une prostatectomie totale, afin d’évaluer la tendance Française à partir de 2 centres universitaires de haut volume chirurgical.

**Méthodes.** – Il s’agissait d’une étude rétrospective, multicentrique où toutes les PT réalisées, dans 2 centres universitaires Français et quelque soit la voie d’abord, laparoscopique ou rétropubienne, pour chacune des années 2005, 2010 et 2015 étaient incluses. Les données préopératoires (âge, PSA, stade clinique, nombre de biopsies positives, score de biopsie de Gleason) et postopératoires (pTNM, score de Gleason pathologique (pGS)) ont été analysées et comparées.

**Résultats.** – Au total, 1282 PT ont été réalisées (503 en 2005, 403 en 2010, 376 en 2015). Respectivement entre 2005, 2010 et 2015, le nombre médian de biopsies positives a augmenté significativement de 2,30 vs 2,88 vs 5,3 ( $p=0,0001$ ). La répartition des risques selon la classification de D’Amico évoluait avec le temps avec : un risque faible : 49,9 vs 44,4 vs 15,7 % ( $p=0,0001$ ) ; risque intermédiaire : 40,95 vs 43,92 vs 64,1 % ( $p=0,0001$ ) ; et risque élevé : 9,15 vs 11,66 vs 20,2 % ( $p=0,0001$ ) entre 2005, 2010 et 2015 respectivement. Le score pGS évoluait vers un score plus élevé avec SG < 7 : 22,8 vs 29,9 vs 7,1 % et SG  $\geq$  7 : 77,2 vs 70,1 vs 92,9 % ( $p=0,001$ ). De plus les stades pTNM évoluent avec notamment une extension extraprostatique : pT2 : 66,9 vs 51,9 vs 48,7 % ; pT3 : 33,1 vs 48,1 vs 51,3 % ( $p=0,0001$ ).

**Conclusion.** – Cette étude a montré un changement dans la prise en charge du CaP depuis les nouvelles recommandations sur le dépistage du PSA et l’évolution des traitements conservateurs. Le nombre de PT pour les CaP à risque plus élevé augmente. Ce changement correspond à une meilleure sélection des patients éligibles à la PT : diminution pour les maladies à faible risque et augmentation pour les maladies localisées à haut risque.

**Niveau de preuve.** – 3.

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## Introduction

Prostate cancer (PCa) incidence increased significantly since the establishment of PSA screening in the 1980s [1]. In this context, age, PSA and clinical stage at the diagnosis decrease for patients treated by radical prostatectomy (RP)

[2]. Moreover, the pathological results after RP reported an increasing rate of organ-confined disease from 50% to 80% in USA between 1988 and 2001 and from 50% to 75% in Europe between 1988 and 2005 [3]. After an increase in the rate of RP and debate about the risk of overtreatment, there is currently a decrease in the number of RP in France from

25,000 per year between 2009 and 2011 to 19,600 in 2014 [4] whereas the absolute number of RP from 5 European institutions increased from 2344 to 2504 patients between 2010 and 2015 [5]. Gallina et al. [3] in USA and recently Budaus et al. [6] in Germany reported a stage migration to higher risk and non-organ-confined disease, from 30% to 45% in USA between 2001 and 2005 and from 19 to 33% in Germany between 2003 and 2009. Beauval et al. observed the same trend with more pT3 on pathological results between 2005 and 2010 from a French cohort [7]. Even more recently, a European multicenter analysis showed a decrease in the percentage of patients having only localized Gleason 6 disease after surgery from 34% in 2005 to 8% in 2015 for all patients with a corresponding increase in the proportion of patients with locally advanced disease ( $\geq$  pT3 and/or Gleason  $\geq$  7) from 66% to 92% over the same years. The same study also reported a decrease in the percentage of patients who were eligible for active surveillance from 54% to 38% between 2005 and 2015 [5].

The objective of this study was to observe the migration of pathological stages from patients undergoing radical prostatectomy over 10 years, to see the contemporary trend in 2 French referral tertiary institutions.

## Methods

For this study, the RP databases were retrospectively collected from 2 high volume tertiary referral institutions, were combined and analyzed for each of the 3 years, 2005, 2010, 2015. Between 2005 and 2015, 1282 patients with localized prostate cancer were treated by RP after approval from our Institutional Review Board (503 RP in 2005, 402 RP in 2010, 376 RP in 2015).

## Treatment

All patients were treated with RP associated or not with extended pelvic lymph-node dissection. RP were performed by laparoscopic, robot-assisted or open retropubic prostatectomy.

## Endpoint

All complete clinical and pathologic data were recorded, including age, year of surgery, preoperative PSA, clinical stage, biopsy Gleason score, number of biopsy cores, number of positive cores, percentage of positive biopsy cores, pathologic stage, pathologic Gleason score, seminal-vesicle invasion, surgical-margin status, and lymph-node invasion. The clinical stage was assigned according to the 2002 TNM staging system, prostate biopsy cores were obtained under transrectal ultrasound guidance, using a >12-core biopsy protocol, and some were realized using an image fusion system (Koelis, guided-biopsy) and pre-treatment PSA was measured before digital rectal examination. Dedicated genitourinary pathologists assessed biopsy and pathologic grading in each center without central pathology review according to the Gleason grading system before 2005 and the modified ISUP Gleason score after 2005. There analyzed the prostate to the Stanford protocol and the pT stage according to the 2002 AJCC staging system for PCa.

Patients were stratified using the D'Amico classification, in low, intermediate and high-risk of progression. Low-risk PCa was defined as:  $\leq$ cT1a, cN0/X, cM0/X and PSA <10 ng/mL, and clinical Gleason 6 disease. Intermediate risk was defined as: cT2b or PSA  $\geq$  10 and  $\leq$  20 ng/mL or clinical Gleason score = 7. High-risk disease was defined as:  $\geq$ cT2c, cN1, cM1, PSA >20 ng/mL, and/or clinical Gleason  $\geq$  8. Any of these criteria would make a patient to be considered high risk. Organ confined disease was defined as:  $\leq$  pT2 and ISUP 1 (Gleason score 6) whereas no organ confined was > pT2 or  $\geq$  ISUP 2 ( $\geq$  Gleason 7). Gandaglia and al in 2015 defined patients with a better prognosis (pT2 and GS  $\leq$  6) who would be eligible for active surveillance in whom surgical treatment may be questionable, or in a conservative approach [8].

## Statistical analysis

Data were summarized using descriptive statistics. Categorical variables were presented as contingency tables into the statistical software, i.e, number and percentage for each category of variable, and number of missing data. Continuous variables were presented as median, range, and number of missing data. Comparisons between groups were performed using the Chi-squared or Fisher's exact test for categorical variables and the student t test or Anova for continuous variables. All reported p-values were two-sided with a significance level at  $P < 0.05$ . Statistical analysis was performed using PRISM (GraphPad Prism® version 5.0, Software, Inc, California, USA).

## Results

The absolute number of RP performed including these 3 years (2005, 2010, 2015) was 1282. For the year 2005, 503 RP were realized, in comparison to 403 RP in 2010 and 376 in 2015, which corresponded to a 19% decrease in RP between 2005 and 2010 and 25% between 2005 and 2015.

The clinical and pathological characteristics are summarized in Table 1.

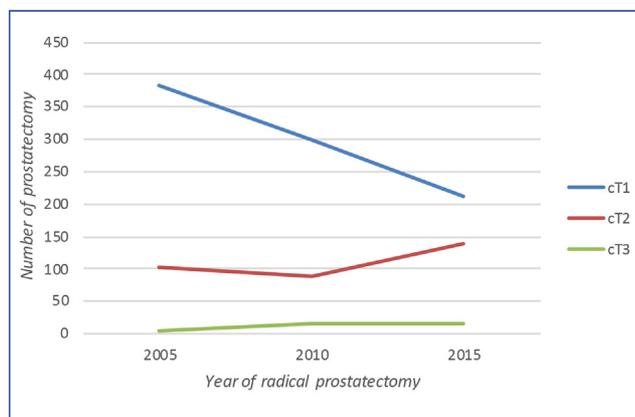
The preoperative median PSA increased from 8.55 ng/mL to 8.99 ng/mL and 10.14 ng/mL ( $P=0.047$ ) respectively in 2005, 2010, 2015. The median number of positive cores increased significantly from 2.29 in 2005 to 2.86 in 2010 and 5.3 in 2015 as well as the biopsy GS  $\geq$  7 which increased from 46.8 in 2005 to 76.3% in 2015.

The clinical stages were significantly different and cT1c decreased from 77.8% in 2005 to 73.0% in 2010 and 57.5% in 2015 ( $P=0.0001$ ) while cT2 increased from 20.7% in 2005 to 23.0% in 2010 and 37.9% in 2015 ( $P=0.0001$ ). Also cT3 increased from 1.0% in 2005 to 4.0% in 2010 and 4.6% in 2015 ( $P=0.0001$ ) (Fig. 1).

Specimen GS increased significantly to GS  $\geq$  7, from 77.2% in 2005 to 70.1% in 2010 and 92.9% in 2015 ( $P=0.0001$ ). Mainly, the pathological stages evolved towards non-localized tumors, with a decrease of pT2 from 66.9% to 51.9% and 48.7% ( $P=0.001$ ) and an increase for pT3 from 33.1% to 48.1% and 51.3% ( $P=0.0001$ ), respectively in 2005, 2010 and 2015 (Fig. 2). Thus, in 2015, more pT3 (51.3%) than pT2 were observed (48.7%).

**Table 1** Clinical and pathological characteristics of patients according to the date of surgery.

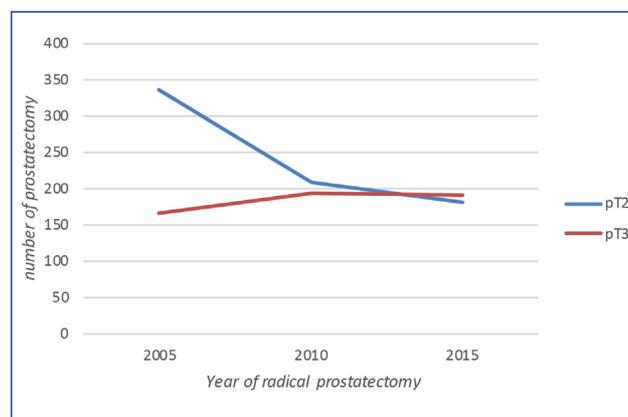
	2005	2010	2015	P
Age (yr)	62.85	62.52	64.48	0.0001
PSA (ng/mL)	8.55	8.99	10.14	0.047
Number of positives cores	2.2	2.8	5.3	<0.0001
Biopsy Gleason Score (n)				
< 7	302 (63.0)	242 (60.3)	88 (23.7)	< 0.0001
7	154 (32.0)	136 (33.9)	246 (66.3)	
> 7	24 (5.0)	23 (5.7)	37 (10.0)	
cTNM (n, %)				
T1c	383 (77.4)	298 (74.0)	211 (57.5)	< 0.0001
T2a	82 (16.7)	58 (14.4)	97 (26.4)	
T2b	20 (4.0)	27 (6.7)	32 (8.7)	
T2c	0 (0)	4 (0.9)	10 (2.6)	
T3	5 (1.0)	16 (4.0)	17 (4.6)	
T4	2 (0.4)	0 (0)	0 (0)	
Pathologic Gleason score				
< 7	113 (22.8)	118 (29.4)	26 (7.0)	< 0.0001
7	336 (67.9)	247 (61.4)	303 (81.9)	< 0.0001
> 7	46 (9.3)	37 (9.2)	41 (11.1)	0.6
pTNM (n, %)				
pT2a	42 (8.3)	32 (7.9)	23 (6.2)	0.37
pT2b	43 (8.5)	7 (1.7)	6 (1.6)	< 0.0001
pT2c	250 (49.7)	170 (42.2)	152 (40.9)	0.013
pT3	166 (33.0)	194 (48.1)	191 (51.3)	< 0.0001
pT4	2 (0.4)	0 (0)	0 (0)	
Prostate volume (cc)	55.56	48.86	53.27	0.0001



**Figure 1.** Evolution of clinical stage cTNM in patients treated by radical prostatectomy.

After stratification, according to D’Amico’s risk groups, there was a significant reduction in the proportion of low-risk PCa from 49.9% in 2005 to 44.4% in 2010 and 15.7% in 2015 ( $P < 0.0001$ ) and therefore a significant increase towards high-risk PCa from 9.1% in 2005 to 11.6% in 2010 and 20.2% in 2015 ( $P < 0.0001$ ). (Fig. 3). Therefore in 2015, we had more RP for high-risk than low-risk.

We also observed in detail, the evolution of each parameter of the D’Amico high-risk classification (PSA, cTNM, GS biopsy) for each of these 3 years. Thus, we found that for the high-risk group, the proportion of Gleason 8-10 increased from 14 patients (30.4%) in 2005 to 27 patients (35.5%) in 2015 ( $P = 0.003$ ). There was no significant difference in



**Figure 2.** Evolution of pathological stage pTNM in 10 years after radical prostatectomy.

the proportion of patients  $\geq$  cT2c ( $P = 0.051$ ) or those with PSA  $> 20$  ng/mL ( $P = 0.06$ ) (Fig. 4).

According to Gandaglia stratification, we observed a significant decrease of “favorable pathology” from 21.1 to 19.4 and 5.0% in 2005, 2010 and 2015 respectively (Fig. 5).

## Discussion

There is a confirmed decrease of the numbers in RP while our study concern 2 high volume tertiary referral institutions. Van den Bergh et al. observed unlike an increase of absolute number of RPs based on 5 tertiary European centers

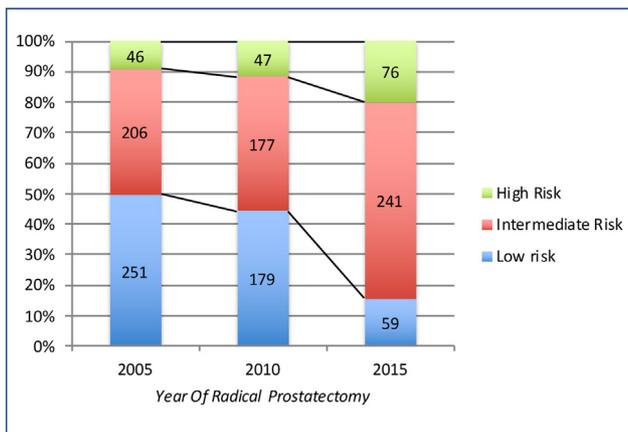


Figure 3. Evolution of D'Amico's risk group in 10 years.

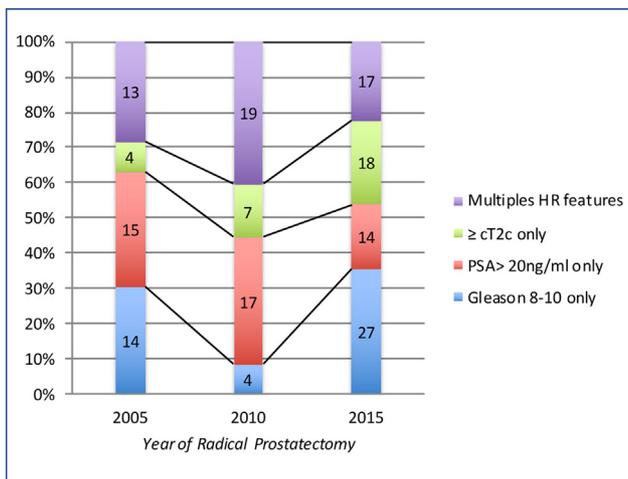


Figure 4. Evolution of high-risk D'Amico's group items.

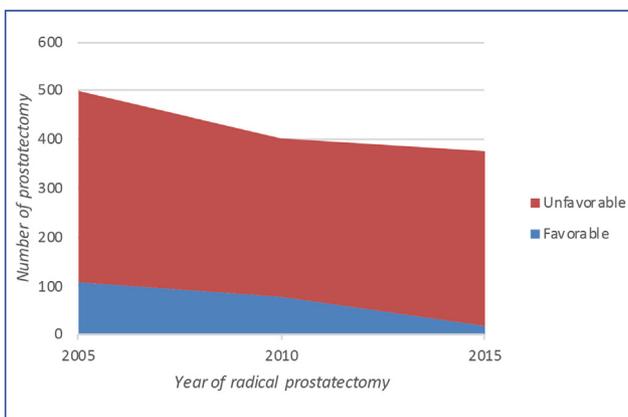


Figure 5. Evolution of favorable/unfavorable groups according to Gandaglia nomogramm.

between 2000 and 2015. In details, the rate of high-risk PCa (HR PCa) increased around 30% (from 1 in 10 patients to 1 in 3 patients) and even more from Germany and Netherland where the rate de HR PCa represented around 40% of RPs in 2015. In France the results were similar to our study with 20% of HR PCa (from 1 in 10 patients in 2005 to 1 in 5 patients in 2015). Also, our study confirmed a later decreasing in France

of RPs for organ confined disease compared with European studies [5,9]. This trend seemed to start after 2004–2005. To put this timing in perspective, the first reports on AS from the European Randomized Study of Screening for Prostate Cancer and initiation of PRIAS date back to 2006–2007.

The variation in the number of RPs can also be explained because of the large referral centers in others European countries (as Germany with more than 20,000 RPs in 15 years) [5].

We can then assume that the decrease in RP is even greater in other institutions with a variable rate among the French regions testified our result with a decrease of 6.7% between 2010–2015 whereas the decrease of RP in France was 21% between 2008 and 2016 [10]. The global number of RPs increased continuously through 2007 and the drop of 20% between 2007 and 2010 was explained by the stabilization of PCa incidence and the introduction of new recommendations by the French Association of Urology in 2007, highlighting alternative options such as active surveillance and brachytherapy [11,12].

Indeed, the increase in PCa screening led to earlier diagnosis and thus to lower risk diseases, localized to the prostate [2]. These patients are often eligible for active surveillance with an increasing incidence that could partly explain the decrease of RP and especially the risk of overtreatment. These patients will then have a delayed curative treatment when progression [12].

More recently, PCa focal treatment techniques such as HIFU and cryotherapy have been developed which, in the context of protocols, essentially treated patients with low risk of development with an increasing proportion [13,14]. These 2 centers had the possibility to perform focal treatments such as HIFU between 2010 and 2015 or cryotherapy for one of them.

Migration from staging to organ-confined-disease as well as a decrease in age and PSA at diagnosis has been reported since the generalization of PSA screening [2,15]. For the past decade, there has been an inverse migration of the pathological stages of patients treated by RP resulting in an increase of high-grade stage on pathological specimen and GS ≥ ISUP2 [3,5–7,16,17]. This stage migration is well represented in our study where the proportion of low risk decreased considerably since in 2015 a greater number of RP are executed for high-risk PCa (20.2%) than low risk (15.7%) ( $P < 0.0001$ ). The same trend was also observed in a UK regional tertiary referral center over 10 years with an increased proportion of high-risk disease from 11.6% between 2005–2008 to 33.6% between 2013–2015 [17].

This could represent to a better selection of patients, where RP is reserved for higher stages and also a better low risk selection with the development of unfavorable SA criteria such as invasion percentage on biopsy and MRI that are recently applied.

In addition, MRI has an increasingly important role in the diagnosis of PCa with the use of a fusion imaging system in these two centers to perform targeted biopsies. This is reflected in the significant increase in the number of positive biopsy in our study 2.29 to 2.86 and 5.3 respectively in 2005, 2010, 2015 ( $P < 0.0001$ ). Several studies have shown the interest of MRI for the detection of significant cancers in order to carry out biopsy of suspicious areas and do not misunderstand a more aggressive disease (ISUP > 1) [18,19].

Here the use of targeted biopsies started between 2010 and 2015 in these 2 centers and could partly explain the increase in the number of positive biopsies testified by the randomized study PRECISION where the rate of positive biopsies was 44% for targeted biopsies compared to the rate of 18% for standard biopsies. Moreover, this same study observed 38% of significant cancers ( $\geq$  ISUP 2) in the targeted biopsy group against 26% for standard biopsies ( $P=0.005$ ) [20].

The French and European associations of urology have expanded the recommendations for RP for locally advanced stages through a good survival [21,22]. Indeed the specific survival at 5, 10 and 15 years and evaluated between 90–99%, 85–92%, 62–84% and the overall survival at 5 and 10 years was 90–96 and 76–77%, respectively [23–27]. Free-land and al reported a specific survival of 84% at 15 years after RP alone for T3 [25].

Our results could be in line with the current trend of applying this radical treatment only to the most beneficial population and so avoiding side effects to others.

This change in indications of RP is still evolving and currently, local treatment is also developing in diseases even more advanced or metastatic [24,25]. Indeed, RP can be practiced for PCa with clinically pelvic lymph node-positive (cN1) disease to provide local treatment in a multimodal approach. Local treatment  $\pm$  androgen deprivation therapy (ADT) was associated with a significant overall mortality-free survival benefit (hazard ratio = 0.31) and no difference was highlighted between RT and RP [28]. In addition, local control with cytoreductive RP in a context of oligo-metastatic disease may be a part of a multimodal approach in a well-selected population. Some studies observed a significantly better clinical symptom-free survival (38.6 versus 26.5 months) and cancer-specific survival rates (95.6% versus 84.2%) with a similar overall survival compared to ADT alone [29].

In the future, development of new tools will be helpful to evaluate preoperative risk. For example a preoperative nomogram for identification of pathologically favorable disease in intermediate risk has been developed with a strong accuracy (AUC = 82%) [30]. This validated risk calculator can help physician to distinguish favorable intermediate risk PCa that can be treated by conservative approach.

In last decade, several studies investigating diagnostic biomarkers (PCA3, Prostate Health Index, 4K score) with promising results that can help physician in decision-making in challenging clinical settings [31].

Weak points of our study included the fact that this was a multifactorial stage migration as change in screening and diagnosis practice. Indeed the risk distribution can also be explained by the modification of the classification of the Gleason score since 2005 where even a tiny fraction of more aggressive tumor is reported in the final analysis which makes it possible to reclassify a disease towards higher scores [32]. Also, MRI may have reclassified patient as non-confined organ disease with better detection of T3. The increasing use of targeted biopsy may have resulted in finding more high Gleason scores. In addition, we had no objective evidence on the use of other treatments especially for the low risk. We can suggest a higher rate of focal treatment and AS without data to confirm it in our database and some patients may have been initially managed with AS before undergoing surgery. However, the incidence of

PCa remained stable in France, at around 0.4% each year between 2009 and 2014, while a lack of specific treatment (AS or watchful waiting) increased from 20.8% in 2009 to 26.9% in 2012 [4]. This could be an additional argument in favor of a change in the selection of these patients. These results should be taken with caution because this was an observational study evaluating the absolute number of RP and the evolution of the pathological profile of these patients without specifying the proportion of other treatments applied or the number of PCa detected each year.

Finally, our results reflected the practice from 2 tertiary referral institutions and cannot be extrapolated to all others centers that do not necessarily have other treatments available to manage low risk disease. Long-term studies are needed to assess the overall and specific survival of these groups in order to confirm this better patient selection. The potential risk of this high-risk migration would be to miss the window of curability.

## Conclusion

Over the past 10 years, there has been a stage migration to higher risk diseases. In 2015 more RP are performed for intermediate and high risks than low risks. This increase in RP for higher-risk or locally advanced diseases corresponds to improve patient selection and because of recognized efficacy of RP in local control and the emergence of new therapies for low-risk PCa.

## Disclosure of interest

The authors declare that they have no competing interest.

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