Active surveillance in prostate cancer is possible for Afro-Caribbean population: Comparison of oncological outcomes with a Caucasian cohort

La surveillance active du cancer de prostate est possible en population afro-caribéenne : comparaison des résultats oncologiques avec une cohorte caucasienne


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KEYWORDS
Active surveillance; Afro-Caribbean; Prostate cancer; Low risk

Summary
Background. — Prostate cancer is supposedly more aggressive among Afro-Caribbean men. There is a lack of data in this population for active surveillance. Published series are retrospective or have small samples and results are discordant. The objective was to determinate whether actual active surveillance modalities can be applied for Afro-Caribbean men by comparing their oncological outcomes with Caucasian men.
**Methods.** — A total of 449 consecutive patients who underwent active surveillance for favorable-risk prostate cancer in two French University-Medical-Centers between 2005 and 2018: 261 in Guadeloupe, French West Indies, and 188 in Bordeaux, metropolitan France. Median follow-up was 56 months, (95% CI [32–81]) and 52 months (95% CI [30–75]), respectively (P = 0.07). Curative treatment was given in case of histological, biological, or imaging progression, or upon patient demand. Primary endpoints were treatment-free, overall and specific survival. Secondary outcomes were reasons of discontinuating active surveillance, histological poor prognosis factors after prostatectomy, CAPRA-S score, biochemical-recurrence-free after treatment and metastasis-free survival. Kaplan–Meier method was used.

**Results.** — Median treatment free survival was 58.4 months (CI 95% [48.6–83.1]) for ACM and not reached at 120 months for CM (P = 0.002). Overall survival (P = 0.53), and specific survival (P = 0.21) were similar in the two groups. CM were likely to have poor prognosis factor on prostatectomy piece (57 vs 30%, P = 0.01). No difference for repartition of the CAPRA-S score (P = 0.86), biochemical-recurrence-free (P = 0.92) and metastasis-free (P = 0.44) survival.

**Conclusions.** — Oncological outcomes for active surveillance of Afro-Caribbean and Caucasian men were similar in terms of mortality, recurrence and metastasis in our bicentric study, showing usability of current criteria for Afro-Caribbean. The higher rate of disease progression in the Afro-Caribbean population requires close monitoring.

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**MOTS CLÉS**
Surveillance active ; Afro-caribéen ; Cancer de prostate ; Faible risque

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**Introduction.** — Le cancer de prostate (CaP) est d’agressivité supposée plus importante chez les hommes afro-caribéens, avec peu de données concernant cette population en surveillance active (SA). Objectif : comparer l’évolution et l’agressivité des CaP en SA des patients d’origine Afro-caribéenne par rapport aux patients d’origine caucasienne.

**Méthodes.** — Étude bicentrique de 449 patients en SA pour un CaP de risque favorable entre 2005 et 2018: 261 en Guadeloupe, Antilles françaises, et 188 à Bordeaux, France métropolitaine. Le suivi médian était respectivement de 56 (IC 95% [32–81]) et 52 (95% IC [30–75]) mois (p = 0.07). Un traitement curatif était appliqué en cas de progression histologique, biologique, à l’imagerie, et par souhait du patient. Les critères de jugement principaux était la survie sans traitement, globale et spécifique. Les critères secondaires étaient les raisons d’arrêt de surveillance, les critères de mauvais pronostic après prostatectomie, le CAPRA-S score, les survies sans récidive biologique et sans métastases, utilisant la méthode de Kaplan–Meier.

**Résultats.** — La médiane de survie sans traitement était de 58,4 mois (IC 95% [48,6–83,1]) pour le groupe Antillais et non atteinte à 120 mois pour le groupe caucasien (p = 0,002). La survie globale (p = 0,53) et spécifique (p = 0,21) étaient comparables dans les 2 groupes. La présence de critère de mauvais pronostic sur pièce de prostatectomie était plus répandue dans la cohorte caucasienne (57% vs 30%, p = 0,01). Aucune différence en termes de CAPRA-S score (p = 0,86), survie sans récidive biologique (p = 0,92) et sans métastases (p = 0,44).

**Conclusion.** — Les résultats oncologiques sont comparables en termes de mortalité, récidive et métastases pour ces deux populations, montrant la possibilité de la SA en population caribéenne. Toutefois, le taux plus important de progression tumorale nécessite une surveillance rapprochée.

**Niveau de preuve.** — 3.
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**Introduction**

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer death among men worldwide [1]. The development of individual screening has helped to decrease its specific mortality at the cost of over-diagnosis of indolent forms [2]. Active surveillance (AS) is an important option in the management of localized PCa with a low risk of progression [3]. It is proposed for asymptomatic patients in a good general state of health with a life expectancy of more than 10 years. The aim of this con-
servesive strategy is to delay curative treatment, which can be associated with morbidity and a poorer quality of life [4]. Tumor progression needs to be closely monitored to remain curable in case of an unfavorable evolution. The oncological safety of AS has been confirmed in several large international series with a long-term follow-up, up to 20 years [5–7]. Selection criteria for eligible patients have been variable, depending on series [8]. They were based on the results of a digital rectal exam, prostatic specific antigen (PSA), Gleason score, and tumor volume on biopsy. Some studies also took PSA density (PSAd) into account. Most used narrow criteria, inspired by the Johns Hopkins Hospital cohort [9], but AS is also applicable to all low risk PCa [10]. Current guidelines are mainly based on data from Caucasian men [11]. However, the Afro-Caribbean population is known to have a different epidemiology, with one of the highest incidence and mortality rates for PCa worldwide [1,12]. This disparity is explained by several factors, notably African ethnic origin and chlordecone exposure [13]. The incidence, progression, and mortality rates between the Afro-Caribbean and Afro-American populations, as well as that of sub-Saharan African descent, are similar [14]. The rate of tumor progression appears to be higher, with a poorer prognosis, poorer histological characteristics of surgical samples, and a higher rate of biochemical recurrence after prostatectomy for patients with low-risk and very low-risk PCa in AS. However, the results are discordant, and some studies have shown no differences [15,16]. Most series have consisted of the analysis of retrospective data of prostatectomies of low-risk patients who did not undergo AS. In prospective studies of AS, men of sub-Saharan African descent have often been under represented [17]. Furthermore, there is no proof of persistent disparity after adjusting for demographic characteristics at inclusion, type of chosen treatment, and socio-economic status of the patient [3]. The absence of data for this population does not allow the modification of inclusion or follow-up modalities [11]. Here, we sought to evaluate evolution and aggressivity of PCa in AS in the Afro-Caribbean population, and compare it to that of the Caucasian population with equal access to medical care. We analyzed two prospective French cohorts from the University Medical Center (UMC) of Pointe-à-Pitre, West French Indies, and UMC of Bordeaux, Metropolitan France, to determine whether current criteria are usable for men of sub-Saharan descent.

Patients and methods

Population

A total of 449 consecutive patients was enrolled in an AS protocol. 261 men were included in the UMC of Pointe-à-Pitre (Afro-Caribbean group) between March 2005 and May 2018. 188 men were included in the UMC of Bordeaux (Caucasian group) between December 2006 and May 2018. All patients were diagnosed with a localized PCa, mostly of very low risk, defined by the French criteria as PSA ≤ 10 ng/mL, Gleason score of 6 (3+3), and less than three positive cores, with a maximal invasion of 3 mm per core. Some selected patients of low or favorable intermediate risk were also included, after a multidisciplinary oncologic concertation meeting. Low risk was defined as PSA ≤ 10 ng/mL and Gleason score 6 (3+3); favorable intermediate risk as PSA between 10 and 20 ng/mL or Gleason score of 7 (3+4). Patients were followed with digital rectal exam each year and measurement of PSA blood levels each six months. A systematic second prostate biopsy was performed between 6 and 18 months after prostatic and pelvic magnetic resonance imaging (MRI) for histological confirmation. Reevaluation biopsies were performed each 2 years. Pelvic and prostatic MRI were interpreted by an experienced radiologist, using the PI-RADS score, showing a significant lesion with a score between 3 and 5. Criteria for discontinuating AS were biological progression (PSA doubling time < 36 months), an increase in tumoral length core invasion (more than 3 mm or than 50% per core), more than two positive biopsies, a Gleason score ≥ 3 + 4, MRI progression or request of the patient. Various curative treatments were proposed after multidisciplinary oncological concertation, based on the data of clinical, biological, histological and MRI progression: radical prostatectomy (RP), radiotherapy, androgen deprivation therapy (ADT). Concerning focal therapy, brachytherapy was only practiced in Bordeaux and High-Intensity Focal Ultrasound (HIFU) started in Pointe-à-Pitre in 2018.

Statistical analysis

Primary endpoints were treatment-free (TFS), overall (OS) and specific (SS) survival for all patients, by the Kaplan–Meier method for both populations. Secondary endpoints were biochemical -recurrence-free survival (BRFS) after prostatectomy and after all treatment, and metastasis -free survival for all patients by the Kaplan–Meier method, the presence of poor prognosis factors and the CAPRA-S score. Biochemical recurrence was defined as two PSA > 0.2 ng/mL after RP, and/or PSA ≥ Nadir + 2 ng/mL after radiotherapy or focal treatment. Histologically poor prognosis factors for surgical samples were defined as ≥ pT3a (upstage), pH+, Gleason > 3 + 4 and/or R+ status. Biochemical recurrence risk (BRR) after RP was evaluated with the CAPRA-S score, based on pre-operative PSA levels, Gleason score, surgical margins, seminal vesicle extension, and lymphatic invasion assessed by surgery. BRR was considered to be low for a CAPRA-S score from 0 to 2, intermediate if it was from 3 to 5, and if it was ≥ 6. Data are expressed in median, IQR (25–75%) and frequency (%). Categorical variables were compared using the Exact Fisher Test and continuous variables with the Mann Whitney Test. Survivals were compared with the log-rank test. Statistical analyses were performed using jmp pro® 9.0, SAS inc., (SAS campus drive), Cary, North Carolina.

Results

Population

The baseline characteristics were similar between the two groups (Table 1). Median age was 65.6 and 64.6 years for ACM and CM (P = 0.18). 91.2% of ACM were classified as low risk, versus 91.5% for CM (P = 0.07). Median follow-up was 56 months, (95% CI [32–81]) and 52 months (95% CI [30–75]), respectively (P = 0.07), with a maximum follow-up of 13.2
and 10.9 years, respectively. During this period, 67% of CM versus 48% of ACM remained on AS (Fig. 1).

**Treatment**

Comparison of TFS between both populations is exposed in Fig. 2. Median TFS was 58.4 months (CI 95% [48.6–83.1]) for ACM and not reached at 120 months for CM (P = 0.002). The reasons for discontinuating AS were similar in the two groups, in terms of biological and MRI criteria. Concerning histological criteria, there was a significative difference in the increase of tumoral length for 53% of ACM versus 37.1% of CM (P = 0.04) (Table 2). ACM were more likely than CM to experience disease progression (OR = 2.09; CI 95%; [1.39–3.15]). Most patients who underwent treatment had a RP upon discontinuating AS: 81.9% of ACM and 60.8% of CM. Focal treatment was given to 23.5% of CM versus 1.75% of ACM (P = 0.0003). For patients treated by RP, the proportion with one or several poor histological prognostic factors in the surgical samples was greater for CM than ACM, 57.1%.

![Figure 1. Flow chart.](image)

**Table 1** Demographic, clinical, biological, histological, MRI characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Bordeaux</th>
<th>Pointe-à-Pitre</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (year)</td>
<td>64.6 [60.7–67.5]</td>
<td>65.3 [59.8–70.1]</td>
<td>0.18</td>
</tr>
<tr>
<td>Median PSA (ng/mL)</td>
<td>6.24 [4.7–8.07]</td>
<td>5.82 [4.39–7.61]</td>
<td>0.27</td>
</tr>
<tr>
<td>PSA density ≤ 0.15, n (%)</td>
<td>128 (70.72)</td>
<td>164 (62.84)</td>
<td>0.08</td>
</tr>
<tr>
<td>Gleason score on biopsy, n (%)</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>1 (0.53)</td>
<td>3 (1.15)</td>
<td></td>
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<tr>
<td>5</td>
<td>3 (1.60)</td>
<td>9 (3.45)</td>
<td></td>
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<tr>
<td>6</td>
<td>182 (96.81)</td>
<td>243 (93.10)</td>
<td>0.40</td>
</tr>
<tr>
<td>7(3 + 4)</td>
<td>2 (1.06)</td>
<td>6 (2.30)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 positives biopsies, n (%)</td>
<td>7 (4.43)</td>
<td>18 (6.95)</td>
<td>0.29</td>
</tr>
<tr>
<td>Median biopsic tumoral length (mm)</td>
<td>1 [0.6–2]</td>
<td>1 [1–3]</td>
<td>0.0004</td>
</tr>
<tr>
<td>cT2, n (%)</td>
<td>21 (11.17)</td>
<td>46 (17.62)</td>
<td>0.06</td>
</tr>
<tr>
<td>MRI realised, n (%)</td>
<td>146 (77.66)</td>
<td>204 (78.16)</td>
<td>0.90</td>
</tr>
<tr>
<td>Lesion on MRI, n (%)</td>
<td>105 (72.41)</td>
<td>156 (76.85)</td>
<td>0.10</td>
</tr>
<tr>
<td>Lost of follow-up, n (%)</td>
<td>12 (6.38)</td>
<td>15 (5.75)</td>
<td>0.77</td>
</tr>
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</table>
versus 29.9% ($P = 0.01$) (Table 3). The frequency of upstaging was greater for CM than ACM, with 39.29% of pT3 stage versus 14.95% ($P < 0.0001$). There was no significative difference in upgrade between the two groups relative to the initial biopsy ($P = 0.13$). There was also no significative difference between the two populations for stratification by the CAPRA-S score ($P = 0.86$), with low BRR for 57.5% of ACM versus 57.1% of CM (Table 3).

### Mortality and metastasis

OS ($P = 0.42$) and SS ($P = 0.21$) were similar in the two groups (Fig. 3). Three ACM patients died from cardiovascular events and one from pancreatic cancer. One CM died from infection after prostatectomy. MFS was not significatively different between the two groups ($P = 0.62$) (Fig. 4). In the Afro-Caribbean group, two patients showed bone localization. One man had recurrence after RP, with a low CAPRA-S score and a very low risk at diagnosis. The disease of the other evolved during AS. He had a favorable intermediate risk at diagnosis. In the Caucasian group, two patients with an initially very low risk developed metastases during AS.

### Biochemical recurrence

BRFS were similar after all treatment ($P = 0.92$) and after prostatectomy ($P = 0.92$) (Fig. 5). Among the nine ACM who had recurrence after RP, four were treated with radiotherapy, one had only radiotherapy, an others a combination of radiotherapy and ADT, and three had not yet received treatment. Four CM had a recurrence after RP. Three were treated with radiotherapy and one had combination of radiotherapy and ADT. Recurrence after HIFU was treated by RP for one patient and two had not yet received treatment.
Table 3  Anatomo-pathological analysis after prostatectomy.

<table>
<thead>
<tr>
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<th>Bordeaux</th>
<th>Pointe-à-Pitre</th>
<th>P</th>
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<tbody>
<tr>
<td>pT stage, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>pT2</td>
<td>17 (60.71)</td>
<td>74 (85.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pT3a</td>
<td>11 (39.29)</td>
<td>6 (6.90)</td>
<td></td>
</tr>
<tr>
<td>pT3b</td>
<td>0 (0)</td>
<td>7 (8.05)</td>
<td></td>
</tr>
<tr>
<td>pN stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pNx</td>
<td>9 (32.14)</td>
<td>29 (33.33)</td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>18 (64.29)</td>
<td>56 (64.37)</td>
<td>0.93</td>
</tr>
<tr>
<td>pN1</td>
<td>1 (3.57)</td>
<td>2 (2.30)</td>
<td></td>
</tr>
<tr>
<td>R ± , (n %)</td>
<td>4 (14.29)</td>
<td>22 (25.29)</td>
<td>0.22</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
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<tr>
<td>6</td>
<td>10 (33.33)</td>
<td>39 (44.83)</td>
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<tr>
<td>7 (3 + 4)</td>
<td>11 (37.04)</td>
<td>31 (35.63)</td>
<td></td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>6 (18.52)</td>
<td>17 (19.54)</td>
<td>0.40</td>
</tr>
<tr>
<td>8</td>
<td>2 (7.41)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>9</td>
<td>1 (3.70)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>1 or more poor prognosis factor, n (%)</td>
<td>16 (57.14)</td>
<td>26 (29.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Capra-S score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (57.14)</td>
<td>50 (57.47)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (35.71)</td>
<td>28 (32.18)</td>
<td>0.86</td>
</tr>
<tr>
<td>3</td>
<td>2 (7.14)</td>
<td>9 (10.34)</td>
<td></td>
</tr>
<tr>
<td>Upgrade surgery sample relative to initial biopsy, n (%)</td>
<td>20 (71.43)</td>
<td>48 (55.17)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Figure 3.  Overall and Specific survival.

Discussion

AS has a major role in the management of low-risk PCa. However, most studies have been carried out in the Caucasian population [17]. A number of retrospective or small sample series suggest more defavorable outcomes for low-risk PCa in patients of African ethnic origin [18,19]. The aim of our study was to screen the evolution and aggressiveness of favourable-risk PCa on AS in the Afro-Caribbean population through a direct comparison with a Caucasian population.

Our results demonstrate a higher rate of curative treatment for Afro-caribbean men (ACM), with a median treatment-free survival of 58 months versus not reached at 120 months for Caucasian men (CM). Two American series of AS showed that black race was a predictor of treatment for disease characteristics [20,21]. We found two-fold higher risk of progression in ACM. In a multicentric study (Detroit, Cleveland, Guadeloupe), that compared Guadeloupean and Caucasian American men on AS, during a three-year follow-up, the proportion of patients remaining on AS was 66% versus 82%, respectively, with a progression rate that was four times higher in the Caribbean group [19]. Debasish Sundi et al. reported three time more histological progression in follow-up biopsy for Afro-American men than Caucasian patients [22]. Our results and these data highlight the importance of close follow-up for patients of African ethnic origin on AS.

AS is still an important option for patients of sub-Saharan African descent, despite the aggressive features of PCa in this population. Overall and specific survival were excellent and comparable in the two groups, with no specific mortality from PCa in the Afro-Caribbean group and only one death in the Caucasian group from a post-operative infection. The rate of metastasis for all patients was also acceptable, with less than 3% of other localizations for both populations after 5 years of follow up. We recently reported security of AS for our population, in a prospective study, in comparison with international published data [23]. With selected patients, specific survival was 100% with a metastasis rate of 0.4% over four-years median follow-up. In this bicentric study, we
confirmed that global, specific and metastasis-free survival are the same in the two cohorts.

Tumoral aggressivity after prostatectomy in Afro-American patients is still a contentious topic. Most series screening for poor prognostic factors after prostatectomy retrospectively analyzed surgery samples of patients who would have qualified for AS. Afro-American men are more likely to have unfavorable outcomes after surgery, with higher upgrading and upstaging rates, than their white American counterparts [24–26]. A recent study from the SEARCH database, with a large number of Afro-American men who had the same access to healthcare did not find any significant difference between the two populations in terms of histological reclassification or biochemical recurrence after immediate prostatectomy [15]. In contrast, our series showed more upstaging in the Caucasian cohort. This could be explained by a different repartition of curative options to treat localized PCa in the two centers. Indeed, 20% of treated patients in Bordeaux were offered HIFU or brachytherapy, generally proposed for smaller tumoral lesion than prostatectomy. The other 60% of treated patients had a surgical treatment, versus 80% in Guadeloupe, where focal treatments have only lately become available. Nevertheless, the repartition of poor prognostic factors according to the CAPRA-S score and biochemical-recurrence-free survival after prostatectomy and all treatments were comparable, with a five-years biochemical rate of less than 15% for both groups.

Several studies suggest that the higher reclassification rate of African descents may be related to the more anterior localization of significant tumors found in prostatectomy samples [27]. This would lead to under-diagnosis by standard echo-guided prostate biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy. In 2018 at the UMC of Guadeloupe, we analysed prostatic MRI before targeted biopsy.
system®), has been practiced since 2017 in both centers. Biopsies were previously performed with cognitive fusion. Mager et al. showed a learning curve for targeted biopsy, with better detection after 42 procedures [29]. Both centers were at the beginning of the experience during the study.

Our study had several limitations. Ethnic statistics are not allowed in France. Thus, the two groups were not allocated according to the race, but to where the patients live. It is commonly admitted that more than 80% of the population is of African descent [12]. The greater incidence of PCa in this population suggests a larger proportion of ACM in this cohort. This was a retrospective analysis of prospectively collected data. There was no prospective protocol, although the inclusion and follow-up criteria, as well as treatment, were very similar. This was also a bicentric study, with no central pathological or imaging review, which could have caused a bias of histological and MRI interpretation.

The strength of this study is the large proportion of ACM, who represented 58% of the total cohort. These men have the same access to French healthcare as metropolitan patients in terms of diagnosis and treatment of all type of diseases, removing any socio-economic factors. Clinical and pathologic features were comparable at inclusion for the two groups and the criteria used for discontinuing AS were the same, based on French guidelines.

Conclusion

For selected patients with the same access to healthcare, tumour progression in patients under AS for localized prostate cancer was higher for ACM. Treatment-free survival was thus shorter than for CM. However, short- and medium-term oncological outcomes concerning mortality, recurrence and metastasis were similar for the two groups. Furthermore, we did not observe more unfavorable features in surgical samples for ACM. Current recommended modalities of AS can thus be safely applied for all ACM, if they are closely monitored.

Disclosure of interest

The authors declare that they have no competing interest.

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