

## The risk of upstaged disease increased with the body mass index in low risk prostate cancer patients eligible for active surveillance

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## ABSTRACT

Background: Obese patients have a greater risk of adverse pathologic features, of upgrading/upstaging and of biochemical recurrence after radical prostatectomy (RP). The impact of body mass index (BMI) on the risk of misclassification and of differed radical treatment in active surveillance (AS) programs has not been thoroughly assessed.

Objective: To evaluate the impact of the BMI on the risk of misclassification for AS eligibility.

Design, setting, and participants: 230 RP men eligible for AS according to the following criteria: PSA  $\leq 10$ ng/ml, clinical stage T1c, Gleason score  $\leq 6$ ,  $< 3$  positive cores, extent of cancer in any core  $< 50\%$  and a life-expectancy  $> 10$  years.

Intervention: All patients underwent a standardized 21-core biopsy and a RP at our department between January 2001 and December 2010.

Measurements: Misclassification was defined as upstaged disease (pathological stage  $> pT2$ ) and/or upgraded disease (Gleason score 7 or more; primary Gleason pattern 4) in RP specimens. PSA outcomes were also recorded (mean follow-up 20 mo).

Results and limitations: Mean BMI was  $26.4 \text{ kg/m}^2$  and 13% of patients were obese (BMI  $> 30$ ). Mean BMI was the only preoperative factor significantly associated with the risk of upstaged disease. In multivariate analysis, a BMI  $> 30$  remained an independent predictive factor for upstaged disease ( $p=0.003$ ; OR 4.2). The risk of upgraded disease (primary Gleason pattern 4) was significantly decreased by 4.5-fold in large prostate glands  $> 50 \text{ ml}$  ( $p=0.008$ ). The

biochemical recurrence-free survival curves were not significantly different between men with or without overweight ( $p=0.950$ ).

Conclusions: Obese men are at higher risk of upstaged disease with a proportion of 30% of pT3 disease in RP specimens. BMI might be taken into account at inclusion of low risk prostate cancer patients in active surveillance programs. Our results may help urologists to better inform the obese men eligible for AS about this risk of misclassification and to improve treatment decision-making.

## INTRODUCTION

Active surveillance (AS) entails a strategy by which selected men are managed expectantly with the intention to apply potentially curative treatment in case of progression signs [1-4]. Cancers that are amenable to AS usually are identified on favourable preoperative parameters and the risk is estimated by integrating Gleason score, pretreatment PSA, clinical stage, and the extent of biopsy involvement with tumour [5-9]. Published AS series use different criteria largely based on centre experiences and preferences with no hard data. The most common clinical data used to define AS criteria are a Gleason score  $\leq 6$ , PSA  $\leq 10$  ng/ml and a clinical stage T1c disease. The PSA density, and thus indirectly, the prostate volume, is noted as inclusion criteria in some studies with different reported cut-offs for AS inclusion [2,5,10-11]. Other characteristics to consider include pathological biopsy parameters with a wide variation concerning the AS inclusion criteria. Various AS programs include cancers involving  $<3$  cores only [11] and with an extent of cancer in any core  $<50\%$  [2,10]. Studies comparing entry criteria for AS protocols have emphasized the risk of under-diagnosis, adverse pathological findings and thus, missing window of curability if AS is preferred whatever the retained pathologic criterion used [12-13]. However, to our knowledge, no AS protocol has studied the impact of body mass index (BMI) on this risk of misclassification and of differed radical treatment in AS programs. Literature data suggest that in men undergoing radical prostatectomy (RP) increased BMI was associated with adverse pathological features and a greater risk of biochemical progression [14-17].

Based on this lack and on the study facility of the BMI factor, we decided to assess the impact of BMI on the risk of misclassification in terms of non-organ confined and high Gleason score disease in a cohort of men eligible for AS and who underwent a RP.

## MATERIALS AND METHODS

Between January 2001 and December 2010, we identified patients who have undergone a RP for clinically localized and low-risk prostate cancer after a 21-core biopsy scheme at our Department and who were eligible for active surveillance at diagnosis according to the following criteria: PSA level  $\leq 10$  ng/ml, a clinical stage T1c disease, a Gleason score  $\leq 6$ ,  $< 3$  positive cores, an extent of cancer in any core  $< 50\%$  and a life-expectancy  $> 10$  years. The study included 230 men. All patients underwent clinical evaluations, including digital rectal examinations, serum PSA, and transrectal ultrasound. All the patients had undergone a 21-core biopsy protocol as previously described for abnormal digital rectal findings or elevated PSA [18]. All the biopsies and radical prostatectomies were performed in our department and specimens were evaluated by senior uropathologists. Tumour volume was not measured routinely. Data from clinical evaluation, biopsy and RP specimens, and follow-up were recorded in a prospective database. PSA recurrence was defined as PSA  $> 0.2$  ng/ml after RP.

We studied the pathological findings on RP specimens, such as Gleason score, extraprostatic extension (EPE), seminal vesicle invasion (SVI), positive surgical margins, and the PSA outcomes during the follow-up. Correlations between pathological RP features and characteristics at diagnosis (clinical, biological and biopsy pathological data) were assessed. Misclassification was defined as non-organ confined disease (pathological stage  $> pT2$ ) and/or upgraded disease (Gleason score 7 or more; primary Gleason pattern 4) in RP specimens. The qualitative data were tested using a chi-square test or Fisher's exact test as appropriate and the quantitative data were tested using Student's t-test. The Mann-Whitney's test was used in case of no normal distribution. A logistic regression was used to test factors correlated with the risk of misclassification. Analyses were also conducted in a more restrictive cohort of patients after excluding cases with a PSAD  $> 0.15$  ng/ml/gr (Johns Hopkins program criteria) [2]. A linear regression analysis tested the link between BMI and others quantitative variables. Biochemical recurrence-free survival was established using the Kaplan-Meier method. Curves were tested by

log-rank test. The limit of statistical significance was defined as  $p < 0.05$ . The SPSS 13.0 (Chicago, Illinois) software was used for analysis.

## RESULTS

Patient cohort characteristics are shown in **Table 1**. Mean BMI was 26.4 kg/m<sup>2</sup> and 63.5% and 13% of patients had a BMI >25 and >30, respectively.

Biopsy features showed 34.8% of prostate cancers involving 2 cores and a mean total tumor length of 2.5 mm. In RP specimens, a Gleason score 7 or 8 was found in 39.1% of cases.

Extraprostatic extension was reported in 12.2% of cases. Only one case of seminal vesicle invasion was reported. Mean follow-up after surgery was 20 months. Ten biochemical recurrences (4.3%) after surgery were reported during follow-up.

In regression analysis as shown in **Table 2**, a linear correlation was found between BMI, prostate volume (coefficient: 0.231) and PSAD (coefficient: -0.153). BMI was not linearly correlated with age, PSA or total tumor length on biopsies. In multivariate model, the linear link between BMI and prostate volume remained statistically significant (p=0.017).

Correlations between overweight (BMI >25) or obesity (BMI >30) and preoperative features are listed in **Table 3**. No significant differences in terms of age, PSA, total tumor length or number of positive cores. There was a trend towards lower PSAD and larger prostate glands in obese patients but difference did not reach significance.

Correlations between upgraded and/or upstaged disease in RP specimens and preoperative parameters are listed in **Table 4**. Patients with non-organ confined disease in RP specimens had a higher BMI (28.0 versus 26.2 kg/m<sup>2</sup>) compared with those with pT2 disease (p=0.015). No significant difference was reported concerning the others parameters: age, PSAD, PSA, prostate volume, total tumor length and number of positive cores. PSAD was higher (0.146 versus 0.110 ng/ml/gr; p<0.001) and prostate volume (49.1 versus 60.2 ml; p=0.002) was lower in men with Gleason >6 cancer in RP specimens compared with patients without disease upgrading. A primary Gleason pattern 4 cancer was more frequently found in RP specimens of men with a high

PSAD (0.169 versus 0.118 ng/ml/gr;  $p=0.002$ ) and a low-volume prostate gland (41.5 versus 57.6 ml;  $p=0.004$ ).

In univariate analysis, obesity (BMI >30) was significantly correlated with extraprostatic extension. Thirty percent of obese patients had a pT3-4 disease in RP specimens compared with only 9.5% in non obese patients ( $p=0.004$ ; OR 4.1; 95% CI: 1.6-10.1). Prostate volume and PSAD were significantly associated with the risk of upgraded disease (**Table 5**). In multivariate analysis taking into account BMI, prostate volume and PSAD (**Table 5**), a BMI >30 remained an independent predictive factor for a pT3-4 disease in RP specimens. Obese patients had a risk of upstaged disease increased by 4.2-fold compared to their normal or overweight counterparts ( $p=0.003$ ; 95% CI: 1.65-10.64). BMI did not predict upgraded disease. The risk of upgraded disease with a primary Gleason pattern 4 in RP specimen was significantly decreased by 4.5-fold in large prostate glands >50 ml ( $p=0.008$ ; 95% CI: 0.17-0.68). Analyses in a more restrictive cohort (after excluding cases with a PSAD > 0.15 n/ml/gr) showed similar findings with a greater risk of upstaged disease in obese patients (OR 3.5,  $p=0.019$ ; **Table 5**).

In multivariate regression analysis taking into account age, BMI, PSA, PSAD, prostate volume, number of positives cores and total tumor length as quantitative variables, BMI remained significantly predictive for upstaged disease with a  $p$  value of 0.005.

The biochemical recurrence-free survival curves were not significantly different between men with or without overweight (log rank test:  $p=0.950$ , **Figure 1**). Various cut-offs of prostate volume or PSAD did not impact on survival curves.

## DISCUSSION

Active surveillance is a treatment option for selected patients with low-risk PCa. Epidemiologic data demonstrate that the proportion of low-risk men electing surveillance has risen in recent years [19]. Oncologic outcomes from prospective AS programs have validated active surveillance as a safe alternative to immediate curative treatment in carefully selected men [3-4]. Published AS series used different inclusion criteria largely based on centre experiences and preferences with no hard data but with similar outcomes in terms of risk of differed treatment. These inclusion criteria focused on age, PSA, digital rectal examination, PSA density and biopsy parameters. No series has studied the impact of BMI as inclusion criterion. However, literature data suggest that obese RP patients were more likely to have lower recurrence-free survival rates than non-obese patients, suggesting a higher risk of experiencing prostate cancer progression [14-17]. This greater risk of biochemical progression might be explained by a greater risk of adverse pathologic features and of upgrading/upstaging in obese patients [20]. To our knowledge, this risk has not been thoroughly studied in AS series.

The aim of our retrospective study was to compare the rate of misclassification (upstaged and/or upgraded disease) according to the BMI factor in cohort of low risk prostate cancer patients eligible for AS. Each patient underwent the same 21-core biopsy protocol under local anaesthesia and thus, the impact of biopsy core number did not introduce selection bias [21].

The overall results of our series confirmed that a cancer of low grade and small volume in biopsies was not necessarily indicative of a good pathological assessment in RP specimens. The Gleason score was upgraded in 39% of cases and a non-organ confined disease was found in 12.2% of RP specimens. No pathological parameter (number of positives cores, total tumor length) was able to improve this risk assessment.

Our findings suggested that the inclusion of BMI as selection criterion might provide additional significance. In our cohort, obese patients were more likely to have unfavourable disease in RP specimens and had a risk of unsuspected pT3-4 disease increased by 4.2-fold compared to their normal or overweight counterparts. Thirty percent of obese patients had a pT3-4 disease in RP specimens compared with less than 10% in non obese patients. In spite of the linear correlation

between prostate volume and BMI, the predictive value of BMI remained independently significant in multivariate models. The use of PSA density as AS criterion (Johns Hopkins program criteria) did not modify our results.

The proportion of obese patients was not negligible (13%). Moreover, authors have demonstrated that the proportion of patients receiving non-surgical therapies such as active surveillance increased relative to radical prostatectomy for increasing obesity [22]. Thus, the proportion of obese patients in men including in AS programs might be larger than that reported in our RP series.

Concerning the biochemical recurrence after RP, the estimate risk of relapse was comparable and not significantly different according to the BMI cut-offs. The PSA failure after RP can not be an ideal endpoint when addressing oncologic outcomes in AS programs. However, as long as long-term oncologic outcomes will not available from patients managed with AS, the misclassification rate and the biochemical-free survival rates of patients initially managed by RP but eligible in AS protocol will represent important study points of AS strategy analysis.

The next studies should better identify the subgroup of overweight men who benefit most from extensive or magnetic resonance imaging-guided biopsy strategies. The prostate volume has to be considered. Smaller prostate glands have been demonstrated to be associated with adverse pathology and a worse prognosis [23]. Our findings confirmed these results. Another step will probably be to integrate urine prognostic markers such as prostate cancer gene 3 to better characterize the potential aggressive behaviour of supposed low-risk prostate cancers [24-25].

Obese and low-volume prostate glands patients might be an interesting target cohort.

Our results do not contraindicate the inclusions of obese men in AS protocol. AS protocols always included a close surveillance scheme, aiming to catch the aggressive tumors as soon as possible during follow-up. The initial assessment of the misclassification risk is important for patient management and treatment decision; however, it is surely not the best end point to address conclusion in men eligible for AS. Nevertheless, our findings can help urologists to better inform the patients about the risk of misclassification (30%) and the need of close surveillance.

Identifying men with potentially higher risks due to obesity may improve treatment decision-making.

## CONCLUSIONS

For treatment decisions and inclusion of patients in AS protocols, clinicians have to deal with the body mass index of their patients. Compared with normal or overweight men eligible for AS, obese men are at higher risk of upstaged disease with a proportion of 30% of pT3 disease in RP specimens. Impact of obesity on this upstaging risk is independent of prostate volume which significantly impact on the risk of upgraded disease. As the proportion of patients receiving non-surgical therapies such as active surveillance increased relative to radical prostatectomy for increasing obesity, our results may help urologists to better inform the obese men eligible for AS about this risk of misclassification and to improve treatment decision-making.

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## LEGENDS

Table 1. Clinico-biological and pathological characteristics of the overall cohort (n=230).

Table 2. Linear correlation between BMI (as quantitative variable) and the others quantitative parameters: univariate and multivariate analyses.

Table 3. Correlations between BMI (as qualitative variable: cut-offs 25 and 30) and clinico-pathological parameters.

Table 4. Factors associated with a upstaged (>pT2 disease) and/or upgraded (pathological Gleason score 7 or more; primary Gleason pattern 4) disease in RP specimens.

Table 5. Logistic regression analysis testing the relationship between BMI, prostate volume, PSAD and the risks of upstaged/upgraded disease.

Figure 1. Recurrence-free survival curves after RP stratified by the BMI (cut-off 25).