Intermediate-risk Prostate Cancer—A Sheep in Wolf’s Clothing?

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Abstract

This case-based discussion describes a 65-year-old man newly diagnosed with International Society of Urological Pathology (ISUP) grade 2 prostate cancer (PCa). According to the European Association of Urology classification system, the patient harbors an intermediate-risk cancer. In step-by-step discussion, we elaborate guideline-based treatment modalities for intermediate-risk PCa focused on debating active surveillance versus active treatment. Thereby, we discuss the importance of patient characteristics, including age, hereditary factors, life expectancy and comorbidity status, findings of multiparametric magnetic resonance imaging, as well as prostate-specific antigen (PSA) density and PSA kinetics, in predicting the clinical course of the disease. In addition, we focus on cribriform pathology as a predictor of adverse outcomes and critically discuss its relevance in patient management. Lastly, we outline genomic stratification in ISUP 2 cancer as a future tool to predict PCa aggressiveness.

Patient summary: Based on current guidelines, patients with intermediate-risk prostate cancer are treated actively or can alternatively undergo an active surveillance approach when favorable risk factors are present. One major issue is to discriminate between patients who benefit from an active therapy approach and those who benefit from a deferred treatment. Therefore, reliable biomarkers and early predictors of disease progression are needed urgently.

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1. Clinical case presentation

A 65-year (yr)-old man with no previous comorbidities presented at the Department of Urology due to a serum prostate-specific antigen (PSA) elevation of 6.5 ng/ml, with a free PSA (fPSA) level of 12.8%. Concerning his family history, a first-degree relative, was diagnosed with metastatic prostate cancer (PCa) at the age of 57. The patient himself had a tumor-negative prostate biopsy 20 years ago (PSA 2.9 ng/ml, fPSA 13%). The PSA velocity (PSAV) was 3.36 ng/ml/yr (three independent PSA measurements within 9 months (mo)) with a Prostate Health Index (PHI) of 63. The patient was suffering from lower urinary tract symptoms with an International Prostatic Symptoms Score (IPSS) of 7, and no signs of inflammation or infection either in the urine or on digital rectal examination (DRE), which was even not suspicious of prostatic malignancy. In addition, the patient underwent, 3 mo previously, a 1.5 Tesla multiparametric magnetic resonance imaging (mpMRI) scan of the prostate showing, according to Prostate Imaging Reporting and Data System score version 2 (PI-RADS V2), a PI-RADS 2 lesion and no suspicion of clinically significant cancer.

Considering the risk factors of PSA variables (total PSA, fPSA, PSAV, and PHI), the patient underwent mpMRI guided transrectal ultrasound guided prostate biopsies (ten systematic and five targeted according to the T2 sequence in the mpMRI).

Histology demonstrated an acinar and focal cribriform adenocarcinoma of the prostate in two of 15 cores (one mpMRI targeted and one systematic) at the tumor apex left and right lobes, classified as International Society of Urological Pathology (ISUP) grade 2, Gleason grade (GG) 7a (3 + 4) with 5% pattern 4.

Therapeutic options were discussed with the patient, and he decided to select a surgical radical treatment option. Thus, a radical prostatectomy (RP) with pelvic lymphadenectomy (ten lymph nodes removed) and bilateral sparing of the neurovascular bundle was undertaken without intra- or postoperative complications. Histology confirmed an acinar and cribriform adenocarcinoma of the prostate GG 7a (3 + 4), ISUP 2, pT2c, NO (0/12), L0, V0, Pn1, R0. Six weeks after surgery, his PSA was not detectable (PSA <0.01 ng/ml), and the patient had satisfactory urinary continence and erectile function.

2. Guideline-based treatment recommendations for intermediate-risk PCa

Summarizing the clinical case, the patient was diagnosed with ISUP 2 intermediate-risk PCa according to the current guidelines (2021 edition) released from the European Association of Urology (EAU; Table 1) leading to different therapeutic options for the patients (reviewed in Table 2).

Importantly, besides the EAU other associations, such as the National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), and European Society of Medical Oncology have specific guidelines, the main discrepancy of which regarding the treatment is the definition of localized PCa, as different threshold values for the TNM stage, PSA values, and GG were used to determine the different risk groups. Table 1 summarizes the definition of intermediate-risk PCa in the corresponding guidelines. Of note, NCCN and AUA guidelines stratify intermediate-risk PCa into favorable and unfavorable disease [1]. This specific differentiation allows better discrimination of intermediate-risk PCa, leading to the fact that more people can undergo a personalized optimized treatment approach.

2.1. Active surveillance

The Prostate testing for cancer and Treatment (ProtecT) trial comparing active monitoring, RP, and external-beam radiation therapy with neoadjuvant androgen deprivation included 34% of patients with ISUP grade >1 cancer and 10% of patients with PSA levels >10 ng/ml [2]. At a median 10-yr follow-up, outcomes of the trial showed no significant differences in disease-specific or all-cause mortality among treatment groups in patients with intermediate-risk cancer [3], and no difference in mortality among patients with low- versus intermediate-risk PCa was observed. However, early radical treatments reduced the rates of disease progression and metastasis by half compared with active monitoring, with no differences between surgery and radiotherapy. Interpreting these data, one also has to consider that patients in the ProtecT trial were monitored actively, consisting of 3-monthly PSA measurements in the 1st year of the study, followed by testing every 6–12 mo thereafter, that is, not exactly very same as standard active surveillance protocols. Further, in the ProtecT study, men with an increase of at least 50% during the previous 12 mo were reviewed again for management options including active treatment options [3].

Yet, based on this trial, recommendations have been endorsed by the American Society of Clinical Oncology and the recent DETECTIVE consensus meeting for actively monitoring patients with a PSA level of <10 ng/ml and low core positivity [4,5]. Further, there was a consensus at the DETECTIVE meeting that PSA density (PSAd) is an inclusion criterion and intraductal and cribriform histology is selected as an exclusion criterion for active surveillance. Admittedly, patients have to be informed that ISUP grade 2 is associated with a threefold increased risk of metastases compared with ISUP grade 1 [6–8].

2.2. Surgery

Both the SPCG-4 and the PIVOT trial compared RP with watchful waiting including intermediate-risk PCa patients. Briefly, in the SPCG-4 study, death from any cause, death from PCa, and distant metastases were significantly reduced in intermediate-risk PCa by RP, while in the PIVOT trial, RP significantly reduced all-cause mortality, but not death from PCa at an average of 19 yr [9,10]. However, the 22-yr follow-up demonstrated that survival differences favored surgery among men with intermediate-risk disease [11].
Table 1 – Summary of intermediate-risk classification among different guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Intermediate risk without further classification</th>
<th>Favorable intermediate risk</th>
<th>Unfavorable intermediate risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN</td>
<td>No high- or very-high-risk features</td>
<td>No high- or very-high-risk features</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No more than one intermediate-risk factor:</td>
<td>Two or three of the intermediate risk factors:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2b to T2c</td>
<td>T2b to T2c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or</td>
<td>Grade group 2 or 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade group 2 or 3</td>
<td>PSA 10–20 ng/ml And</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade group 1 or 2 And</td>
<td>Grade group 3 And/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage of positive biopsy cores &lt;50%</td>
<td>50% of positive biopsy cores</td>
<td></td>
</tr>
<tr>
<td>AUA/ASTRO/SUO</td>
<td>ISUP 1, PSA 10–20 ng/ml, T1–T2a</td>
<td>ISUP 2, PSA &lt;10 ng/ml, T2b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISUP 2, PSA &lt;10 ng/ml, T1–T2a</td>
<td>ISUP 3, PSA &gt;20 ng/ml, T2b, any T1–2</td>
<td></td>
</tr>
<tr>
<td>EAU</td>
<td>PSA 10–20 ng/ml</td>
<td>ISUP 2, PSA 10–20 ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or GG 7 (ISUP grade 2/3)</td>
<td>Or T2b</td>
<td></td>
</tr>
<tr>
<td>ESMO</td>
<td>T2b and/or GG 7</td>
<td>And/or PSA 10–20 ng/ml</td>
<td></td>
</tr>
</tbody>
</table>

ASTRO = American Society for Radiation Oncology; AUA = American Urological Association; c = clinically; EAU = European Association of Urology; ESMO = European Society of Medical Oncology; GG = Gleason grade; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; SUO = Society of Urologic Oncology.

Table 2 – Overview on EAU guidelines 2021–based recommendations for the treatment of intermediate-risk prostate cancer

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance</td>
<td>Weak</td>
</tr>
<tr>
<td>Offer AS to highly selected patients with ISUP grade 2 disease (ie, &lt;10% pattern 4, PSA &lt;10 ng/ml, (cT2a, low disease extent on imaging and biopsy) accepting the potential increased risk of metastatic progression.</td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer RP to patients with intermediate-risk disease and life expectancy of &gt;10 yr.</td>
<td></td>
</tr>
<tr>
<td>Radiotherapeutic treatment</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer low dose rate brachytherapy to intermediate-risk patients with ISUP grade 2 with (33% of biopsy cores involved, without a recent transurethral resection of the prostate and with a good International Prostatic Symptom Score.</td>
<td></td>
</tr>
<tr>
<td>For IMRT plus IGRT, use a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 wk or 70 Gy/28 fx in 6 wk), in combination with short-term ADT (4–6 mo).</td>
<td>Strong</td>
</tr>
<tr>
<td>In patients not willing to undergo ADT, use a total dose of IMRT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 wk or 70 Gy/28 fx in 6 wk) or a combination with brachytherapy.</td>
<td>Weak</td>
</tr>
<tr>
<td>Other therapeutic options</td>
<td>Weak</td>
</tr>
<tr>
<td>Only offer whole-gland ablative therapy (cryotherapy, high-intensity focused ultrasound, or focal ablative therapy) for intermediate-risk disease within a clinical trial.</td>
<td></td>
</tr>
<tr>
<td>Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.</td>
<td>Weak</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; AS = active surveillance; EAU = European Association of Urology; fx = fractions; Gy = Gray; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; RP = radical prostatectomy.

Importantly, interpreting the findings of these trials, one has to be aware that RP was compared with watchful waiting that cannot be on a par with active surveillance.

2.3. Radiation therapy

For external-beam radiation therapy, a cumulative dose of 76–78 Gray or moderate hypofractionation in combination with short-term neoadjuvant plus concomitant androgen deprivation therapy (4–6 mo) is recommended [12]. In addition, low dose rate brachytherapy can be offered to highly selected patients (ISUP grade 2 with <33% of biopsy cores involved with cancer) without recent transurethral resection of the prostate and good IPSS. Furthermore, fractionated high dose rate brachytherapy can be offered as monotherapy to selected patients with intermediate-risk PCa, although they should be informed that results are available only from small series at very experienced centers [13].

2.4. Experimental therapeutic approaches

Focal therapies such as high-intensity focused ultrasound therapy, cryotherapy, photodynamic therapy, electroporation, or cyber knife robotic radiosurgery system technology are currently not recommended outside of clinical trials due to the lack of sufficient prospective evaluation.
3. Implication of comprehensive evaluation for therapy decision

Guidelines from the EAU, AUA, as well NCCN in the USA, and the UK National Institute for Clinical Excellence (NICE) recommend that active surveillance can be offered to selected intermediate-risk PCa patients.

However, summarizing current literature and clinical practical experience, one major issue is to reliably discriminate between patients with intermediate-risk disease who profit from an active therapy approach and those who benefit from a deferred treatment [14].

Although many trials demonstrated that ISUP grade 2 PCa can be monitored safely, there are also contradictory findings concerning the risk of tumor progression in ISUP 2 PCa. For example, it has been demonstrated in an RP cohort that ISUP 2 disease was associated with a threefold greater risk of non-organ-confined disease compared with ISUP 1 disease [15]. In addition, there is evidence that almost one-third of patients with favorable ISUP 2 cancer harbor disease of higher grade or higher stage than their biopsy and clinical examination suggest [16].

Considering the therapeutic options to treat actively or not, it is important for clinicians to seek as much additional prognostic information as possible in order to give in-depth advice to the patient. In the particular case described herein, the main patient and tumor characteristics are discussed to facilitate treatment decision.

3.1. Patient characteristics

Almost 75% of PCa cases are diagnosed in men above the age of 65 yr, mirroring the strong correlation between PCa incidence and increasing age. Results of autopsy studies have shown that almost 30% of men over the age of 50 yr have histological evidence of PCa [17]. Outcomes from the Surveillance, Epidemiology, and End Results (SEER) database, following conservative management among men with localized PCa, demonstrated that 15-yr PCa mortality rates among men with GG 5–7 were age dependent, varying from 5.7% (64–74 yr) to 10% (≥75 yr). Therefore, most guidelines recommend age-related PSA thresholds for the detection of clinically significant PCa, and patient’s age should be a strong parameter in the treatment decision-making for intermediate-risk disease as well as a family history of prostate and breast cancer.

Large epidemiological studies describe that family history is an important risk factor for PCa. First-degree relatives are exposed to a higher risk than second-degree relatives, with a relative risk varying from 2.5 for men with one first-degree relative to 7.7 for men with more than three affected relatives [18] Furthermore BRCA1/BRCA2 mutations appear to confer an increased risk of aggressive disease. Some publications, however, report that family history does not increase the risk of PCa progression during active surveillance except for patients with African-American ethnicity [19,20].

It is further important to assess the life expectancy and the comorbidity status of the patient. In the SPCG-4 trial, 29-yr follow-up data comparing RP versus watchful waiting confirmed that patients with long life expectancy benefited from RP, with a mean of 2.9 yr of life gained [21]. Of importance, one has to consider that life expectancy varies among different countries. Of note, the 15-yr outcome of a population-based study following conservative management of men over 65 yr with localized PCa demonstrated that patients with a high comorbidity score had lower PCa-specific mortality rates because of deaths from competing risks [22].

3.2. Multiparametric MRI

Based on the PRECISION trial, where detection of clinically significant cancer was increased upon mpMRI use compared with transrectal guided biopsy, current EAU guidelines recommend performing mpMRI before prostate biopsy even in biopsy-naïve men. The incorporation of mpMRI in the diagnosis of PCa has further implications in the selection of intermediate-risk PCa patients appropriate for active surveillance [23]. A recent meta-analysis including 4265 patients reported pooled detection rates for clinically significant PCa and all PCa of 4% and 17% for PI-RADS 1–2, 17% and 33% for PI-RADS 3, 46% and 63% for PI-RADS 4, and 75% and 90% for PI-RADS 5 lesions, respectively [24]. In addition, findings of the PRECISE trial revealed that patients without radiological progression during active surveillance have a very low probability of clinical progression [25]. However, the Canary Prostate Active Surveillance Study (PASS) investigators found in a large cohort of men on active surveillance, who subsequently underwent mpMRI-targeted biopsy, that 11% harbored GG ≥2 PCa within the targeted lesion, while 13% had GG ≥2 PCa outside of it [26]. In fact, mpMRI was more sensitive in detecting ISUP grade ≥2 than ISUP grade 1 PCa, particularly evident for small size PCa considering cancers smaller than 0.5 cm [27]. Thus, several studies focus on the improvement of mpMRI findings in the active surveillance setting, for example, by implementing imaging findings in risk calculators. For instance, the risk calculator by Gandaglia et al [28] was designed to improve the selection of intermediate-risk PCa patients suitable for active surveillance by incorporating mpMRI findings. Summarizing the findings of this trial, the use of this risk score resulted in an absolute increase of 10% in the number of patients eligible for active surveillance and was validated recently [29].

3.3. PSAd and PSA kinetics

Kotb and colleagues [30] analyzed PSAd in an active surveillance cohort including even patients with GG 7 cancers and found that PSAd is a reliable clinical parameter to predict the behavior of clinically localized PCa in patients under active surveillance. The authors suggest that cases with PSAd <0.15 ng/ml can be followed up safely on active surveillance, whereas those with PSAd of >0.15 ng/ml are at a higher risk of tumor progression and may be better managed by radical therapy. As mentioned before, even in the DETECTIVE meeting, there was a
consensus that PSAd is an inclusion criterion for undergoing active surveillance in intermediate-risk PCa patients. However, no specific cutoff for PSAd was agreed on in this meeting.

In addition to PSAd, PSAV is widely used to detect PCa and predict disease progression. However, a recently published systematic review highlighted that results are conflicting regarding the role of PSAV in predicting progression in patients suitable for active surveillance. Currently, there is no evidence to support the use of PSAV in treatment decision for intermediate-risk PCa [31].

3.4. Cribriform histology

It is nowadays evident that GG alone does not account for prognostic differences among various Gleason pattern 4 subtypes, including cribriform, poorly formed, fused, and glomeruloid cancers. Therefore, in 2014, the ISUP and the World Health Organization approved a new PCa grading system for standard histopathological reporting, which reflects the natural course and prognosis of PCa better than previous scoring systems.

3.4.1. Clinical outcomes

Iczkowski et al [32] reported for the first time that a cribriform growth pattern has an independent prognostic value for postoperative biochemical recurrence after RP. In line with this finding, many groups demonstrated the predictive value of a cribriform pattern for adverse pathological findings such as extraprostatic extension and unfavorable outcomes including disease-specific and cancer-specific survival [33]. In addition, studies have demonstrated that GG 2 PCa without cribriform and intraductal carcinoma have similar survival rates to GG 1 PCa and could therefore be considered as low-risk disease [34]. These findings have important ramifications for expanding active surveillance candidates among intermediate-risk PCa patients.

3.4.2. Pathologists’ intraobserver variability

Another important issue related to the studies of prognostic significance of GG 4 subtypes is the lack of uniformity in the definition of microscopic morphology of cribriform PCa associated with high intraobserver variability [35–37]. In order to overcome this issue, Ambrosini et al [38] introduced a deep learning method to detect such patterns automatically via a convolutional neural network trained to detect cribriform growth patterns on prostate needle biopsies. Briefly, the proposed method has 90% sensitivity for detecting cribriform growth patterns. Thus, quantification computer-aided analysis and restrictive morphological and quantitative criteria may improve the performance and real-world clinical utility of pathological reports in the future. Moreover, center-specific outcomes and predictive value of cribriform growth need to be monitored.

3.4.3. Genetic and epigenetic determinants of aggressiveness

Although it is clear that cribriform morphology is associated with unfavorable clinicopathological factors, its genetic features are understood incompletely. Genetic, transcriptional, and epigenetic features of invasive cribriform carcinoma tumors were compared with noncribriform GG 4 using The Cancer Genome Atlas (TCGA) cohort. Remarkably, cribriform carcinomas had distinctive molecular features such as increased somatic copy number variations, increased SPOP and ATM mutations, enrichment for mTORC1 and MYC pathways by gene expression, and increased methylation of selected genes [39]. Moreover, it has been demonstrated that cribriform/intraductal growth is associated with increased genomic instability clustering to genetic regions involved in aggressive PCa, including PTEN, CDH1 or gain of MYC. Somatic copy number alterations comprised 1299 gene deletions and 369 amplifications in the TCGA dataset, of which 474 and 328 events were validated independently [40]. The presence of cribriform histology was moreover associated with an increased genomic risk analyzed using the Decipher assay, a genomic classifier based on expression patterns for 22 RNA biomarkers [41].

3.4.4. Imaging in cribriform PCa

Of note, a comprehensive analysis of cribriform morphology on mpMRI/ultrasound fusion biopsy correlated with RP specimens demonstrated that only 17.4% of cribriform tumors were visible on mpMRI [42]. In addition, there is evidence that a significant proportion of cribriform or intraductal tumors are located in the anterior gland and are likely to be missed on standard biopsy [43]. In order to overcome this problem, Gao and colleagues [44] recently developed a nomogram combining clinical characteristics and mpMRI parameters for the prediction of cribriform morphology in intermediate-risk PCa patients. The cribriform-risk nomogram was developed with the three parameters PSA, PI-RADS score, and maximal biopsy GG, and demonstrated considerable discrimination efficacy (sensitivity 79.2%, specificity 84.0%).

Owing to the poor performance of mpMRI regarding identification of cribriform morphology, advanced imaging techniques are warranted. For example, positron emission tomography (PET) with prostate-specific membrane antigen (PSMA) ligands (eg, 68Ga-PSMA-11) is a nuclear imaging modality currently used predominantly for the detection of recurrent PCa. A recent study including 49 PCa patients demonstrated that 68Ga-PSMA PET/computed tomography effectively identifies the aggressive cribriform morphology in PCa, as SUVmax was a significant predictor of cribriform morphology in PCa [45].

4. Genomic stratification of ISUP 2 cancer

Recent studies report genetic changes associated with unique molecular subtypes and demonstrated that underlying genetic signatures were better predictors of clinical outcomes than GG or PSA values. In addition to studies on key genetic alterations such as fusions of TMPRSS2 with ETS family genes, amplification of the MYC oncogene, deletion and/or mutation of PTEN and TP53, as well as amplification
and/or mutation of the androgen receptor, numerous serum- and urinary-based studies are underway to identify biomarkers predicting tumor aggressiveness. Several trials such as the Prospective Stockholm3 Active Surveillance trial (STHLM3AS) incorporate mpMRI for genomic biomarkers in active surveillance protocols to select appropriate patients [46]. Concerning the discrimination of ISUP 2 cancers, Falagario et al. [47] examined whether the combination of mpMRI and Deciper PCA test helps identify patients with favorable intermediate-risk PCa considered for active surveillance. The authors reported that the addition of the Deciper test to mpMRI imaging improves the prediction of adverse and favorable pathologies. More recently, a urine-based biomarker assay for PCa risk stratification has been established using a 14-gene panel (PMP22, GOLM1, LMTK2, EZH2, GSTP1, PCA3, VEGFA, CST3, PTEN, PIP5K1A, CDK1, TMPRSS2, ANXA3, and CCND1). Taken together, this urine test represents a promising noninvasive tool for the detection of unfavorable PCa in order to facilitate treatment decision in patients with intermediate-risk PCa [48].

5. Summary and conclusions

Although guidelines recommend active surveillance as an option for selected intermediate-risk PCa patients, it is essential to acknowledge current controversies in defining the optimal candidates for active surveillance. Clinical assessment is multifactorial and relies on the evaluation of risk factors, including age, comorbidity status, PSA kinetics, imaging in the form of mpMRI, and accurate histopathological reporting, in order to offer individual patients an active monitoring option.

Further research is needed to gain a deeper understanding of the molecular characteristics of intermediate-risk PCa to predict disease progression using complementary genomic or epigenetic biomarkers. To receive active monitoring or a form of radical treatment is a combined decision between each patient along with his partner and his treating physician. Each decision has to be driven by a well-informed patient, and careful evaluation of the “tradeoff” between oncological outcomes and side-effect profiles of available treatment options.

Author contributions: Isabel Heidegger 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: Heidegger, Roupret.
Acquisition of data: Heidegger.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Heidegger, Roupret.
Critical revision of the manuscript for important intellectual content: All authors.
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Supervision: Roupret.
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