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European Association of Urology

Kidney Cancer

Clinical and Pathological Features Associated with Chromophobe Renal Cell Carcinoma Recurrence: Analysis from a Nationwide Cohort

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Article info

Article history:
Accepted October 31, 2025

Associate Editor:
M. Carmen Mir

Keywords:
Renal cell cancer
Chromophobe carcinoma
Nephrectomy

Abstract

Background and objective: Chromophobe renal cell carcinoma (chRCC) is a rare renal malignancy with a generally favourable prognosis. However, a subset of patients experiences recurrence, which remains poorly characterised. This study aims to identify the clinicopathological factors associated with recurrence in chRCC, describe the timing and anatomical patterns of recurrence, and develop a predictive model to guide surveillance strategies.
Methods: We conducted a multicentre retrospective cohort study using data from the French UroCCR database, including patients treated surgically for non-metastatic chRCC between 2010 and 2024. Clinicopathological features, recurrence-free survival (RFS), cancer-specific survival, and overall survival were

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https://doi.org/10.1016/j.euros.2025.10.023

Prognosis
Recurrence-free survival

analysed. Kaplan-Meier survival curves and multivariable Cox proportional-hazard models were used to assess prognostic factors.
Key findings and limitations: Among the included 683 patients, 43 (6.3%) developed recurrence, with median RFS of 142 mo (95% confidence interval [CI] 121–not reached). Local recurrence was observed in 30 patients, while 18 developed distant metastases, predominantly in the retroperitoneal lymph nodes and lungs. Male sex (hazard ratio [HR] 3.1, 95% CI 1.27–7.54, $p = 0.01$), locally advanced disease (HR 1.94, 95% CI 1.02–3.84, $p = 0.05$), positive surgical margins (HR 3.03, 95% CI 1.4–6.56, $p = 0.005$), and lymphovascular invasion (HR 2.08, 95% CI 1.01–4.38, $p = 0.05$) were independently associated with recurrence. Limitations include the absence of a central pathological review and of standardised recurrence management strategies across centres.
Conclusions and clinical implications: This study provides novel insights into the recurrence patterns of chRCC, highlighting the key prognostic factors. The proposed predictive model was designed to aid clinicians in identifying high-risk patients, optimising follow-up intensity, and guiding therapeutic decisions.
Patient summary: We studied a rare kidney cancer type, called chromophobe renal cell carcinoma (chRCC), to understand why some patients experience recurrence. We found that being male, having advanced disease, or some aggressive pathological characteristics increased the risk of cancer coming back. Our results suggest that doctors should monitor certain patients more closely after surgery. This research may help improve long-term follow-up and treatment plans for patients with chRCC. While certain factors are associated with a higher risk of recurrence, it is important to note that chromophobe renal cell carcinoma generally has a favourable prognosis, and the absolute risk of recurrence remains low for most patients.

1. Introduction

Chromophobe renal cell carcinoma (chRCC) constitutes approximately 5% of renal malignancies and represents a distinct histopathological entity [1]. First described by Thoenes et al. [2] in 1985, chRCC is characterised by large polygonal cells with pale eosinophilic cytoplasm and perinuclear halos [3]. Despite its relatively indolent nature, chRCC can recur and progress to metastasis in a subset of patients, presenting challenges in risk stratification and clinical management [4].

Recent advances in molecular biology and genomic sequencing have provided insights into the genetic aberrations underlying chRCC. Recurrent chromosomal losses involving chromosomes 1, 2, 6, 10, and 17, as well as somatic mutations in *TP53* and *PTEN*, have been implicated in its pathogenesis [5,6]. These findings have prompted a re-evaluation of prognostic factors and potential therapeutic targets.

Although chRCC is generally associated with a more favourable prognosis than other renal cell carcinoma subtypes [7,8], a subset of patients develops recurrence and metastases, significantly impacting survival and quality of life. The clinical behaviour and treatment response of recurrent chRCC remain poorly characterised, necessitating further investigation.

Hence, the ChromoCare study (UroCCR n°136) aims to explore statistical associations between clinical and pathological factors and oncological outcomes to refine risk stratification and inform follow-up strategies.

2. Patients and methods

2.1. Study design

The UroCCR network is a French multicentre observational cohort database that prospectively collects data from patients with kidney tumours. The inclusion criteria were as follows: (1) histologically confirmed chRCC, (2) non-metastatic status at diagnosis, and (3) surgical treatment between 2010 and 2024. Patients were excluded if they had metastatic disease at presentation or missing histopathological confirmation of chRCC. Demographic and clinical variables, staging, histopathological features, recurrence, and survival rates were evaluated.

2.2. Data collection

Preoperative data included the following:

1. Demographic and clinical variables: age, body mass index, comorbidities, Charlson score, smoking habit, number of tumours, tumour diameter, tumour location, and RENAL score
2. Biological variables: blood creatinine and estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula

3. Intraoperative variables: type of surgery (partial vs total nephrectomy) and surgical approach (open vs laparoscopic *vs* robotic)
4. Postoperative variables: pathology specimens were evaluated by a uropathologist in each institution and staged according to the TNM classification. Pathological reports must have included the type of RCC, its localisation, size, the presence of lymphovascular invasion, necrosis, sarcomatoid, or rhabdoid contingent. Finally, local or distant recurrence, cancer-specific mortality, and overall mortality on follow-up were recorded for survival analyses.

2.3. Outcomes

The primary objective was to describe recurrence-free survival (RFS), defined as the time from surgery to the first documented recurrence (local or distant). We secondly analysed the rates of metastatic-free survival (MFS; time from surgery to the first documented distant metastasis), cancer-specific survival (CSS; time from surgery to patient death caused by the index cancer), and overall survival (OS; time from surgery to patient death). For RFS and MFS, patients without an event were censored at the last date of bone or computed tomographic scan. For CSS and OS, patients without an event were censored at the date of the last follow-up. The secondary objectives were to (1) evaluate the timing, localisation, and management of recurrences, and (2) establish the factors associated with the recurrence of chRCC. Finally, we sought to build a risk stratification tool to distinguish high-risk patients of recurrence to guide clinical practice.

Local recurrence was defined as tumour regrowth in the ipsilateral renal bed (after radical nephrectomy) or residual kidney (after partial nephrectomy). Distant recurrence included all extrarenal metastatic sites (comprising the retroperitoneal lymph nodes). Contralateral renal tumours were considered multifocal metachronous disease and not recurrences. These events were excluded from recurrence-related survival analyses. A biopsy sample with pathological examination was not mandatory if recurrence was adjudicated by multidisciplinary meeting. Recurrence events were recorded by local investigators and discussed in institutional multidisciplinary tumour boards following UroCCR definitions. Central adjudication was not performed, but standard definitions were applied uniformly across participating sites. Finally, follow-up was defined as the time from diagnosis to last updates.

2.4. Statistical analyses

Descriptive statistics were used to explore perioperative and pathological variables. Results for continuous variables are reported as the mean and standard deviation or median and interquartile range (IQR), whereas results for categorical variables are presented as the frequency and proportion.

Kaplan-Meier curves were generated to visualise RFS, CSS, and OS. Multivariable Cox proportional-hazard analyses were performed to evaluate the factors associated with RFS, CSS, and OS; to determine the corresponding hazard ratios (HRs) with their 95% confidence intervals (95% CIs); and to comprise for potential confounding factors. Variables tested in multivariable regression models were those statistically significant on a univariable analysis (ie, gender, multiple tumorectomies, clinical stage, positive surgical margins (PSMs), lymphovascular invasion, multiple tumoural foci at pathological examination, and pathological stage).

To reduce multicollinearity, we constructed a correlation matrix of candidate covariates. When two variables were highly correlated (Pearson $r > 0.70$), the variable considered more clinically relevant and/or with fewer missing data was retained, while the other was excluded from the multivariable models.

All statistical analyses are two sided and conducted at the 5% significance level using R Studio version 4.4.2 2024-10-31 (R Foundation for Statistical Computing, Vienna, Austria). As the dataset had <5% missing data for all variables included in the models, no missing data management strategy was used. Therefore, a complete-case analysis was used.

2.5. Ethics approval and consent to participate

ChromoCare (UroCCR n°136) is an observational, multicentre retrospective cohort study involving an analysis of prospectively collected data from the UroCCR project (NCT03293563). The study has institutional review board approval (CNIL authorisation no. DR-2013-206). All patients received oral and written information about the objectives and methodology of the UroCCR project and provided written consent.

3. Results

3.1. Population

A total of 683 (4.7%) patients were deemed eligible for inclusion across the 14 664 cases screened from the UroCCR database. In all, 395 (58%) patients were male with a median age of 61 yr (IQR 52–70). At initial diagnosis, the median tumour size was 4 cm (IQR 2.7–6.5) and median RENAL nephrometry score was 8 (IQR 6–10). A total of 477 (73%) patients had partial nephrectomy, and 356 (60%) individuals had robotic surgery (including 293 robot-assisted partial nephrectomies; see Table 1). The median follow-up was 32 mo (95% CI 29–36). Of the patients, 45% and 23% have been followed for at least 3 and 5 yr, respectively.

3.2. Survival analysis

At the time of the analysis, 43 patients had recurrence (local or metastatic). The median RFS was 142 mo (95% CI 121–not reached [NR]) and the 5-yr RFS rate was 93% (95% CI 90–96%; see Fig. 1). Thirty patients harboured local recurrence (median local RFS 186 mo, 95% CI 127–NR). Eighteen patients developed distant metastasis (of whom five experienced prior local recurrence), corresponding to a 5-yr MFS rate of 96% (95% CI 94–98%). Nineteen patients died during follow-up (median OS 182 mo, 95% CI 182–NR), including four cancer-related deaths (median CSS NR). After 5 yr of follow-up, 97% (95% CI 95–99%) of the population was still

Table 1 – Demographic, clinical, and pathological characteristics of the population at baseline

	Overall cohort (*N* = 683)
Demographic and clinical characteristics	
Gender, no. (%)	
Male	395 (58)
Age (yr), median (IQR)	61 (52–70)
Charlson score, median (IQR)	2 (1–3)
Active smoking (yes), no. (%)	96 (14)
BMI, median (IQR)	25.8 (23–29)
Arterial hypertension (yes), no. (%)	275 (40)
Diabetes (yes), no. (%)	80 (12)
CKD (yes), no. (%)	38 (5.6)
Tumour size (cm), median (IQR)	4 (2.7–6.5)
RENAL nephrometry score, no. (%)	
Low complexity	145 (29)
Intermediate complexity	210 (43)
High complexity	135 (27)
cT, no. (%)	
T1a	307 (50)
T1b	181 (29)
T2a	63 (10)
T2b	36 (5.8)
T3a	29 (4.7)
cN, no. (%)	
N+	13 (2.6)
Surgical approach, no. (%)	
Open	104 (18)
Laparoscopic	134 (22)
Robotic	356 (60)
Type of nephrectomy, no. (%)	
Partial	477 (73)
Pathological characteristics	
pT, no. (%)	
T1a	298 (45)
T1b	141 (21)
T2a	63 (10)
T2b	24 (3.7)
T3a	134 (20)
T4	2 (0.3)
pN, no. (%)	
N+	8 (3.8)
PSM (yes), no. (%)	104 (16)
Lymphovascular invasion (yes), no. (%)	76 (12)
Coagulative necrosis (yes), no. (%)	126 (19)
Sarcomatoid feature (yes), no. (%)	12 (2.0)
Multiple tumoural foci (yes), no. (%)	48 (8.0)

BMI = body mass index; CKD = chronic kidney disease; cN = clinical N stage; cT = clinical T stage; IQR = interquartile range; no. = number; pN = pathological N stage; PSM = positive surgical margins; pT = pathological T stage.

alive. It was noteworthy that eight patients developed contralateral chromophobe tumours, thus considered "multifocal metachronous disease".

3.3. Localisation and management of recurrence

For patients with distant metastasis, the metastatic disease involved a single site in 78% of the population (14/18). Distant metastases concerned the retroperitoneal lymph nodes ($n = 6$), lungs ($n = 5$), mediastinal lymph nodes ($n = 4$), liver ($n = 3$), bone ($n = 3$), and pancreas ($n = 1$).

Regarding the management of renal bed relapse, local recurrence was treated surgically in 11 individuals, with radiofrequencies in five and cryoablation in three. Only one patient had systemic treatment. It was noteworthy that ten patients with recurrence were monitored without any curative treatment. Among patients managed with surveillance only, no cancer-specific deaths were reported during follow-up. Owing to the small number of metastatic events and treatment heterogeneity, further outcome stratification was not feasible.

Of the 18 cases diagnosed with metastatic disease, 12 had systemic therapy, four had local treatment associated with systemic therapy, and two were deemed eligible for palliative care.

Systemic treatments comprised a combination of immunotherapy and anti–vascular endothelial growth factor (anti-VEGF) agents for ten patients, and anti-VEGF agents alone for six patients. Interestingly, 18 patients had at least two recurrences (local or distant) during follow-up.

3.4. Factors associated with recurrence

Several factors were assessed for their association with recurrence (Table 2). In a multivariable analysis, male sex (HR 3.1 [95% CI 1.27–7.54], $p = 0.01$), PSMs (HR 3.03 [95% CI 1.4–6.56], $p = 0.005$), pathological lymphovascular invasion (HR 2.08 [95% CI 1.01–4.38], $p = 0.05$), or pT3/pT4/pN + disease (HR 1.94 [95% CI 1.02–3.84], $p = 0.05$) were associated with recurrence. Interestingly, the inclusion of patients with multifocal metachronous disease considered as recurrence did not alter the statistical significance of the results.

Based on the multivariable Cox model, the impact of co-occurring risk factors can be estimated by multiplying the individual HRs. For example, a combination of male sex (HR 3.1) and PSMs (HR 3.03) results in an expected HR of approximately 9.3, compared with the reference group (female sex, negative margins, no lymphovascular invasion, and pT2 disease). Similarly, a male patient with pT3/4 disease (HR 1.94) and lymphovascular invasion (HR 2.08) would be expected to have an approximately four-fold increased risk of recurrence.

4. Discussion

The present study, based on a large multicentre cohort from the UroCCR database, provides a comprehensive analysis of the oncological outcomes of localised chRCC treated surgically. The findings confirm the generally indolent nature of chRCC, with high RFS and CSS rates. However, a subset of patients presents with aggressive disease features, resulting in recurrence, frequently late, and, in rare cases, cancer-related death.

With a median follow-up of 32 mo, this cohort demonstrated excellent oncological outcomes, with a 5-yr RFS rate of 93% and a 5-yr MFS rate of 96%. These findings align with the previous reports highlighting the low metastatic potential of chRCC compared with ccRCC [9,10]. Local recurrence was observed in 30 patients, while distant metastases were rare ($n = 18$) but predominantly affected the lymph nodes and lung, consistent with known metastatic patterns of chRCC [7,11,12]. Interestingly, eight patients developed contralateral renal tumours, reinforcing the concept of multifocal metachronous disease rather than true recurrence. Despite these favourable outcomes, the results underline the importance of long-term surveillance. While early recurrences may reflect aggressive biology, late recurrences could suggest either an indolent course or the presence of

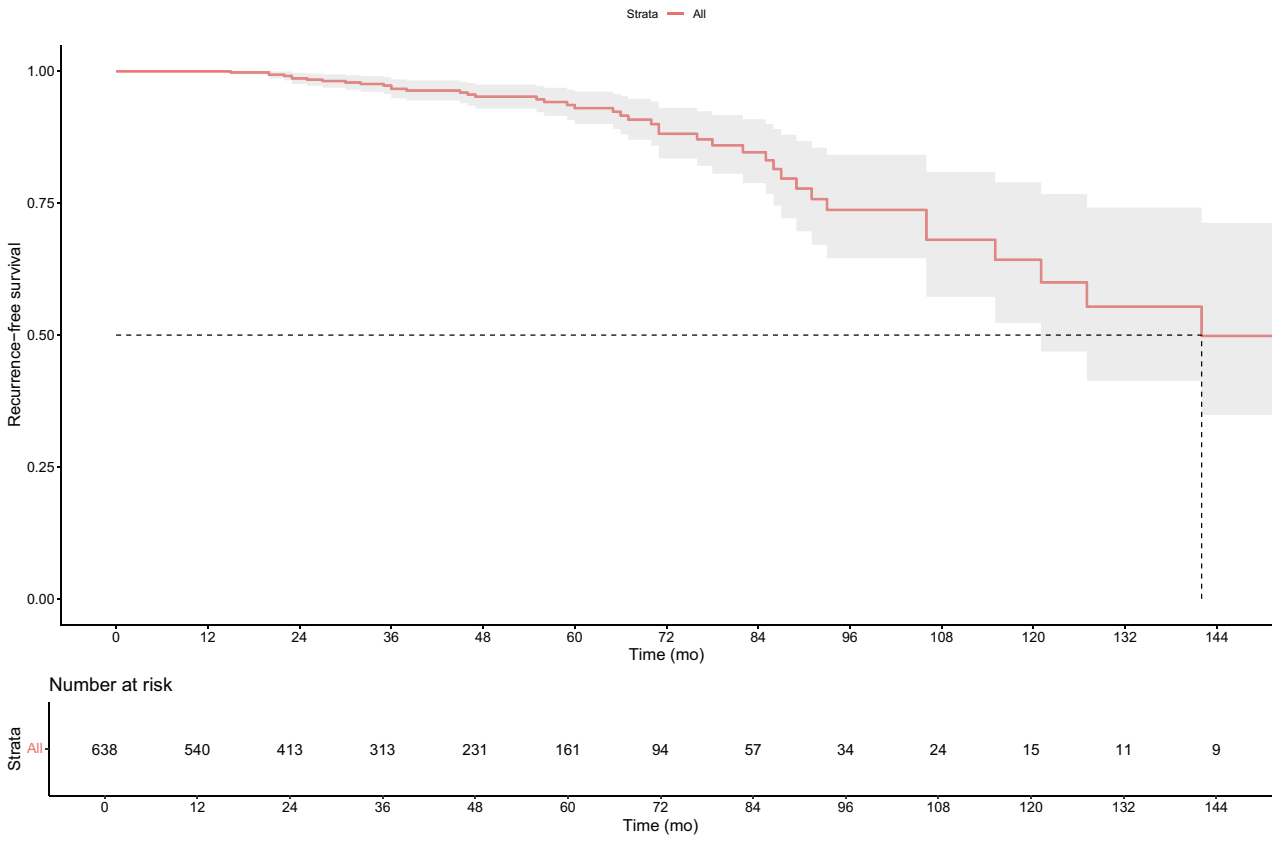

Fig. 1 – Kaplan-Meier curve of the recurrence-free survival.

Table 2 – Univariable and multivariable hazard ratios with their 95% confidence intervals associated with the risk of recurrence

Variable			Univariable		Multivariable	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
Clinical factors	Gender	Male	3.47 (1.54–7.83)	**0.003**	3.1 (1.27–7.54)	**0.01**
	Multiple tumorectomies	Yes	3.78 (1.67–8.09)	**0.001**	–	–
	Surgical approach	Laparoscopy (pure or robot-assisted)	1.17 (0.58–2.38)	0.6	–	–
	Tumour size (cm)	Quantitative	1.07 (0.99–1.17)	0.1	–	–
	Tumour complexity (RENAL score)	High	2.12 (0.98–4.71)	0.06	–	–
	Locally advanced tumour	cT3/cT4 or cN+	5.67 (2.34–13.7)	**<0.001**	–	**–**
Pathological factors	PSM	Yes	3.43 (1.63–7.22)	**0.001**	3.03 (1.4–6.56)	**0.005**
	Coagulative necrosis	Yes	1.53 (0.76–3.08)	0.2	–	**–**
	Lymphovascular invasion	Yes	2.9 (1.43–5.89)	**0.003**	2.08 (1.01–4.38)	**0.05**
	Sarcomatoid feature	Yes	2.33 (0.32–17.3)	0.4	–	–
	Multiple tumoural foci at pathological examination	Yes	2.19 (1–4.86)	**0.04**	–	–
	Pathological stage	pT3/pT4 or pN+	3.02 (1.63–5.6)	**<0.001**	1.94 (1.02–3.84)	**0.05**

95% CI = 95% confidence interval; HR = hazard ratio; pN = pathological N stage; PSM = positive surgical margins; pT = pathological T stage; RFS = recurrence-free survival.
Significantly associated variables with RFS are highlighted in bold characters.

microscopic residual disease at initial treatment. Our findings—where nearly 50% of relapses occurred beyond 5 yr—suggest that limiting follow-up to 5 yr may be insufficient in chRCC patients, particularly in those with aggressive features. Surveillance protocols should consider extending the follow-up period for these high-risk individuals.

The multivariable analyses identified the key factors associated with recurrence, including male sex, lymphovascular invasion, and locally advanced disease at pathological examination. These findings suggest that, despite its traditionally favourable prognosis, chRCC can display aggressive behaviour in a subset of patients. Notably, PSMs and

lymphovascular invasion have been recognised as high-risk features in ccRCC, but their role in chRCC remains poorly defined [1,13–16]. For instance, the prognostic impact of PSMs in chRCC remains controversial. Recent studies have highlighted concerns about local recurrence and the need for more vigilant follow-up in patients with PSMs [17,18]. Our findings reinforce this, as PSMs were independently associated with recurrence, underscoring the importance of surgical technique and postoperative risk stratification. Intriguingly, the sarcomatoid differentiation was not associated with survival outcomes in our cohort likely due to their rarity and possible under-reporting in earlier case, while it has been recognised for its prognostic value in previous studies [11,14]. This may reflect limitations in retrospective pathology reporting across the 14-yr period.

The development of a risk stratification tool incorporating these aggressive features demonstrated a 5.4-fold increased recurrence risk in affected patients, with a stepwise increase in recurrence with the number of risk factors. Our findings suggest that incorporation of chRCC-specific risk factors, such as male sex and lymphovascular invasion, may improve the stratification provided by the existing models such as the Leibovich 2018 score [19]. Although formal validation was beyond the scope of our study, this represents a promising area for future research to tailor surveillance protocols to non–clear cell subtypes.

Among the 43 patients with recurrence, local relapses were primarily managed surgically, with only one patient requiring systemic therapy. In contrast, distant metastases were predominantly treated with a combination of anti-VEGF agents and immunotherapy, reflecting the evolving therapeutic landscape for metastatic non-ccRCC [20–22]. Notably, ten patients with recurrence were monitored without curative intent, none of whom died during follow-up. This suggests that, in select cases, an active surveillance approach may be appropriate, particularly for indolent recurrences. Hence, this study highlights the need for individualised postoperative surveillance strategies in chRCC. While most patients can be monitored safely with routine imaging, those presenting with aggressive features may warrant closer and longer follow-up, and consideration for clinical trials evaluating adjuvant therapy in high-risk RCC subtypes.

Despite its strengths, the present study is not devoid of limitations. First, although the data were prospectively recorded and maintained in a standardised multicentre database, ensuring high-quality data collection, the retrospective design may introduce a selection bias. Second, there was no central pathological review, but the majority of participating centres have expert uropathologists, minimising interobserver variability in the assessment of histopathological features. Moreover, postrecurrence management strategies were diverse, and survival outcomes could not be compared meaningfully across subgroups due to the limited event numbers and treatment heterogeneity. Furthermore, while several associations reached statistical significance, some estimates, such as those for the composite risk variable, were accompanied by relatively wide CIs, reflecting limited precision due to the small number of recurrence events. These findings should therefore be interpreted with appropriate caution and validated (as for the discrimination and calibration metrics) in larger cohorts. Lastly, the relatively short median follow-up may underestimate late recurrences, emphasising the need for extended surveillance studies. Future research should focus on refining risk stratification tools incorporating molecular and genomic markers to identify high-risk chRCC patients more accurately [23]. Additionally, external validation studies of such proposed model, as well as prospective trials evaluating adjuvant therapies specifically in chRCC are warranted to determine whether systemic treatment could alter the natural history of the disease in aggressive cases.

5. Conclusions

This large multicentre study confirms the excellent prognosis of localised chRCC following surgical treatment, with low recurrence and cancer-specific mortality rates. However, a subset of patients exhibits aggressive features associated with an increased risk of recurrence, frequently beyond 5 yr. Our proposed risk stratification model could aid in risk stratification, allowing for personalised follow-up and management strategies. Further studies are needed to optimise postoperative surveillance and explore potential adjuvant treatment strategies for high-risk patients.

Author contributions: Arthur Peyrottes 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.

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Drafting of the manuscript: Peyrottes, Auclin, Audenet.
Critical revision of the manuscript for important intellectual content: Auclin, Audenet.
Statistical analysis: Peyrottes, Auclin.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Audenet, Timsit, Méjean.
Other: None.

Financial disclosures: Arthur Peyrottes certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Data sharing statement: Data are available for bona fide researchers who request if from the authors.

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