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Does early disease progression predict survival after first line-treatment of Waldenström macroglobulinemia?

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Abstract

In symptomatic Waldenström macroglobulinemia (sWM) patients, prognosis is assessed with the international prognostic scoring system (IPSSWM). In follicular lymphoma and other B-cell and T-cell lymphomas, disease progression within 24 months (POD24) or (in patients without POD24) after 24 months has been proposed as the start date for stratifying subsequent survival. In the present report, we assessed in a large series of 472 sWM patients, the prognostic value of this new dynamic endpoint already reported in many other lymphomas subtypes. The 3 year subsequent survival for patients with POD24 was 75% and 93% for patients without POD24. In sWM patients, departure from the proportional hazards assumption complicated this analysis. In patients without POD24, the median subsequent

progression-free survival time of 43 months accounted for favorable outcome, whereas survival after progression was not influenced by the time to progression. In addition, sensitivity analysis showed that the baseline IPSSWM score also influenced survival after POD24. In sWM patients, we conclude that the apparent difference in survival after POD24 or the 24 months time-point (in patients without POD24) is mainly explained by the prolonged subsequent progression free survival of latter patients. Indeed, the mortality after progression is not influenced by the time to this event.

1 | INTRODUCTION

Waldenström macroglobulinemia (WM) is characterized by the production of serum monoclonal immunoglobulin M, lymphoplasmacytic bone marrow infiltration, and a high prevalence of somatic mutations in the MYD88 and CXCR4 genes, amongst others.[1] In patients with symptomatic WM (sWM),[2] the prognosis is typically assessed by applying the International Prognostic Scoring System for WM (IPSSWM).[3] The IPSSWM was recently revised.[4] The prognostic role of the molecular landscape in sWM has been reported, but it has not been fully characterized.[5] We previously reported the prognostic role of progression coded as a time-varying covariate in a Cox proportional hazards model in sWM.[6] By choosing to focus on disease progression within 24 months (POD24) in patients with follicular lymphoma, Casulo et al.[7] dismissed the usual landmark approach[8] or a Cox proportional hazards model with POD24 status as a time-varying covariate because of a significant proportion of misleading early deaths, and difficulty in conceptualizing the results, respectively. Instead, Casulo et al. suggested that survival after POD24 was a valid endpoint, with the clock starting for the reference group (without POD24) 24 months after diagnosis (i.e., treatment initiation since the study enrolled only patients who had not undergone initial watchful waiting period). After POD24 and after 24 months, the survival rate at 5 years was 50% for patients with POD24 and 90% for patients without POD24 respectively, with hazard ratio (HR) up to 6.5.[7]

Since then, this new assessment of survival after POD24 or 24 months (in the reference group of patients without POD24) has been used to assess the prognostic role of early progression in many other B-cell lymphoid malignancies,[9,10] as well as T-cell lymphomas.[11] A broad range of differences in subsequent survival of patients with POD24 and patients without POD24 have been reported primarily for B-cell disorders, including marginal zone lymphoma (HR: 19.5),[9] and mucosa-associated lymphoid tissue lymphoma (HR: 2.15–2.42).[10]

Ultimately, survival after POD24 (in patients with POD24) is similar to survival after progression, whereas subsequent survival in patients without POD24 is the addition of progression-free survival (PFS) after 24 months and survival after late progression.

Using exactly the same method previously published in other B-cell lymphoid disorders,[7,9,10] we sought to decipher the prognostic information provided by the assessment of survival after POD24 or 24 months in sWM patients with and without POD24 respectively, while taking into account the baseline prognostic characteristics of the disease, and the treatment received.

2 | PATIENTS AND METHODS

In 2018, 11 centers from the French Innovative Leukemia Organization (FILO) merged their prospectively maintained local databases in order to investigate the outcomes for treated sWM patients who met the international criteria for the diagnosis of WM[1] and for initiating therapy.[2] Treatment initiation criteria are listed in Table 1. All patients gave their informed consent to participation. In line with the French

TABLE 1 Characteristics of the 472 patients with symptomatic Waldenström macroglobulinemia at the time of the first treatment initiation

Characteristic	Number and percentage[a]
Time from diagnosis to 1st treatment, months, median [IQR]	1.45 [0.43–11.2]
≤6 months	325 (69%)
>6 months	147 (31%)
Age, years, median [IQR]	70 [2–77]
≤65	164 (34%)
>65	308 (66%)
Sex	
Male	327 (69%)
Female	145 (31%)
Hemoglobin, g/dL, median [IQR]	9.5 [8.2–11.3]
≤10	284 (60%)
10–11.5	77 (16%)
>11.5	111 (24%)
Missing	6

TABLE 1 (Continued)

Characteristic	Number and percentage[a]
Platelet count, $\times 10^9$/L, median [IQR]	224 [136–308]
≤100%	80 (17%)
>100%	392 (83%)
Serum β-2 microglobulin, mg/L, median [IQR]	3.3 [2.40–4.5]
≤3	169 (41%)
>3	243 (59%)
Missing	61
Serum monoclonal protein, g/L, median [IQR]	21 [11–34]
LDH percentage of upper normal value	75% (58%–94%)
≤100%	319 (81%)
>100%	75 (19%)
Missing	78
Serum albumin, g/L, median [IQR]	37.8 [33.3–42]
<35	146 (37%)
>35	249 (63%)
Missing	77
IPSSWM score	
Low	68 (16%)
Intermediate	157 (39%)
High	181 (45%)
Missing data	66
MYD88 mutation (L265P)	
Present	87 (97%)
Absent	2 (3%)
Missing data	383
First-line treatment[a]	
Rituximab-based	327 (68%)
Dexamethasone-rituximab cyclophosphamide	196
Bendamustine-rituximab	25
Purine analog or alkylator-based	133 (29%)
Other	12 (3%)
Criteria for initiating treatment	
Constitutional symptoms	114 (24%)
Cytopenia	296 (63%)
Bulky disease	119 (25%)
Hyperviscosity	77 (16%)
IgM-related disorders	105 (22%)

Abbreviations: IQR, interquartile range; IPSSWM, International Prognostics Scoring System for Waldenström macroglobulinemia.
[a]Unless otherwise indicated.

legislation on observational studies of routine clinical practice, the study protocol was approved by a hospital committee with competency for research not requiring approval by an institutional review board. The study complied with the MR003 reference methodology specified by the French National Data Protection Commission [*Commission nationale de l'informatique et des libertés* (Paris, France)].

2.1 | Patients management

The baseline prognostic characteristics were summarized by the IPSSWM. Unfortunately, the revised IPSSWM could not be calculated because of missing LDH in a significant number of patients.

When at least one criterion for initiating therapy (according to the international guidelines) had been met, patients were treated and monitored according to local procedures.[6] All patients received immunochemotherapy after July 2002 - mainly the dexamethasone-rituximab-cyclophosphamide regimen, starting in January 2007).[12] If a rapid response was required (e.g., after plasma exchange for hyperviscosity syndrome), the bortezomib-dexamethasone-rituximab regimen was used after January 2009[13] and the bendamustine rituximab regimen was used after May 2014.[14] The IPSSWM was not taken into account for treatment decisions. None of the patients received maintenance therapy. Disease progression was defined according to the international criteria.[15]

2.2 | Statistical analyses

The first endpoint was survival after 24 months (in patients without POD24) or after progression within 24 months (in patients with POD24). Curves were plotted as described above and previously published.[7,9–11] Patients progression-free with less than 24 months of follow-up or who died of an unrelated cause before 24 months were excluded from the analysis, as reported previously.[7,9–11]

In patients without POD24, we also computed (i) subsequent PFS from the 24 month time point and (ii) survival after late progression (after 24 months).

Before any comparison of survival, the proportional hazard assumption (PHA) was checked using the cumulative sums of the martingale residuals and the Kolmogorov-type supremum test with 1000 simulations.[16] In the event of departure from the PHA, separate HRs was assessed after partitioning the time axis at time points determined from the Schoenfeld residuals plots.[17]

Given the observed departure from the PHA with this endpoint, POD24-stratified Cox models of subsequent survival (i.e.,: survival after POD24 in patients with POD24 or after 24 months in patients without POD24) group[7,9–11] were fitted with the covariate of interest, namely the baseline prognostic characteristics of the disease (summarized by the IPSSWM score) and the treatment received (chemotherapy or immunochemotherapy). Then, sensitivity analyses assessed the prognostic role of these two characteristics in separate Cox

models designed for survival after POD24 (in patients with POD24) and for survival after 24 months (in patients without POD24).

In order to understand the difference in subsequent survival of patients with and without POD24, survival after progression was the second endpoint. Survival after early progression (before 24 months, POD24) and late progression (after 24 months) were compared using the log-rank test.[17] Indeed, PHA was not rejected for these analyses (data not shown). We also checked whether the role on survival after progression of the 24 months time-point in time to progression depended on IPSSWM or first line treatment received (chemotherapy or immunochemotherapy).

All analyses were performed with SAS software (release 9.4, SAS Institute, Cary, NC USA).

3 | RESULTS

3.1 | Initial characteristics and outcome

A total of 472 consecutive patients were registered between July 1993 and July 2018. The patients demographic and clinical characteristics and the distribution of events before and after 24 months are summarized in Tables 1 and 2, respectively. Histological transformation occurred in 31 patients (range: 6–149 months; median: 47) after first treatment initiation, (including five before 24 months). With a median follow-up period of 52 months (range: 6–273 months) in survivors, the 5 year survival rate after first treatment initiation was 81% [95% confidence interval (CI), 77%–85%]; 123 patients died (due to WM: 42; unrelated cause: 31; secondary primary malignancy: 13, infection: 7; unknown: 30).

3.2 | Survival after 24 months (patients without POD24) and after POD24 (patients with POD24)

In patients without POD24), the subsequent 3 year survival rate was estimated to be 93% (95% CI: 89%–97%, Figure 1A). In patients with POD24, it was estimated to be 75% (95% CI, 67%–83%, Figure 1B). We identified a departure from the PHA ($p = 0.036$, Table 3). By partitioning the time axis, we observed that the HR differed from 1 during the first 30 months of subsequent survival but not after that time (data not shown).

TABLE 2 Number of events (progression, second treatment initiation, and death) during the study in the whole patient group and in patients treated with chemotherapy or immunochemotherapy

	Whole group	Chemotherapy	Immuno-chemotherapy
Total number of patients	472	145	327
Low and intermediate-risk ISSWM score	225	76	149
High-risk ISSWWM score	181	47	134
Missing data	66	22	44
Patients with <24 months of follow-up and no progression	101	19	82
Death before 24 months	24	10	14
Censored before 24 months	77	9	68
Patients with POD24 (POD24 group)	129	46	83
Death	52	31	21
Censored	77	15	62
Second treatment[a]	104	40	64
No second treatment at last follow-up	25	6	19
Patients without POD24 (reference group)	242	80	162
Death without progression after 24 months	9	3	6
Censored without progression after 24 months	125	17	108
Progression after 24 months	108	60	48
Death	38	32	6
Censored	70	28	42
Second treatment[a]	94	59	35
No second treatment	14	1	13

Abbreviations: IPSSWM, International Prognostics Scoring System for Waldenström macroglobulinemia; POD24, disease progression before 24 months.

[a]Only a subset of patients who progressed met criteria for initiating second line therapy before death or last follow-up.
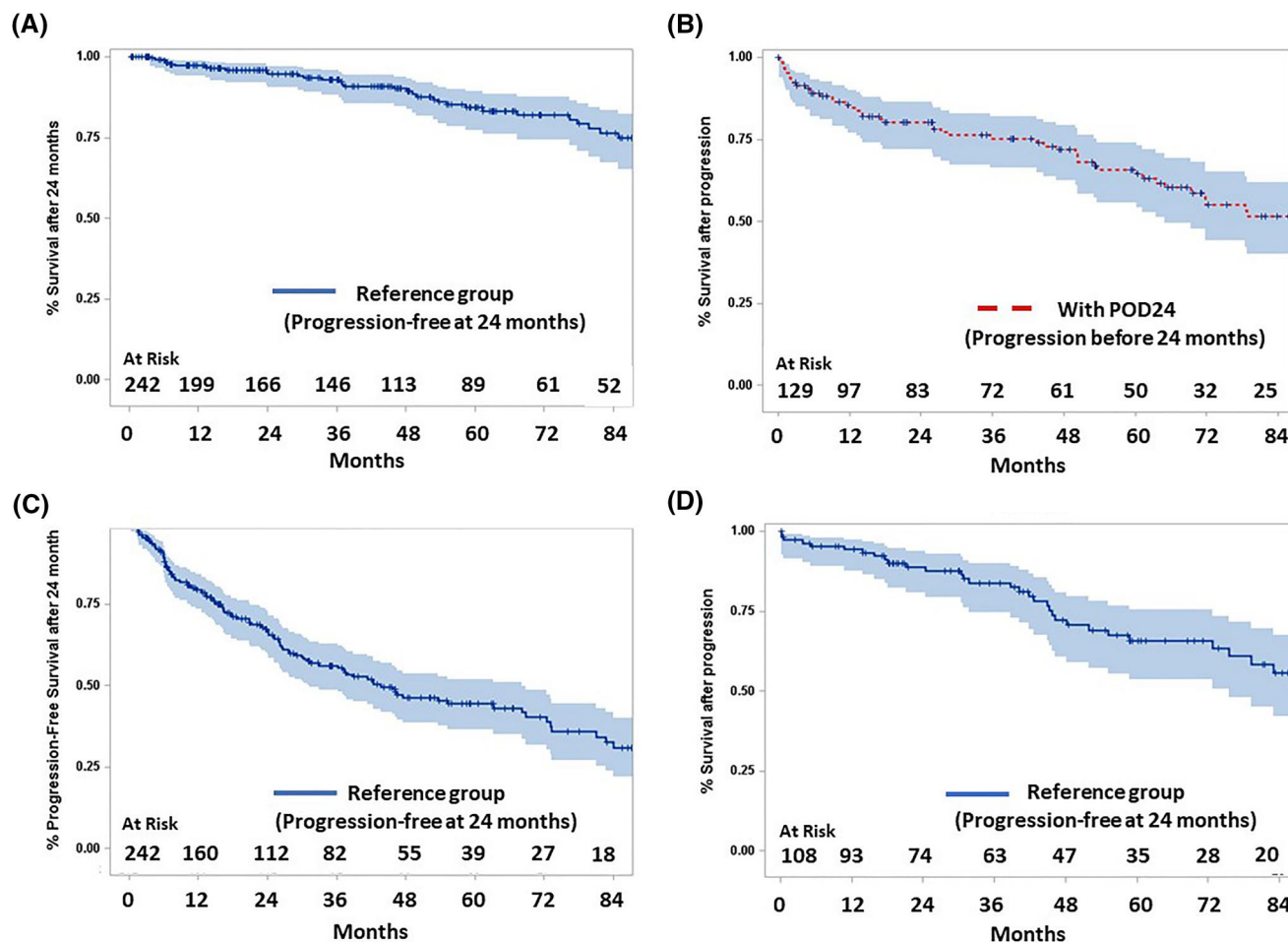
FIGURE 1 Survival from 24 months onwards or after a risk-defining event (progression or relapse before 24 months) in patients with Waldenström macroglobulinemia who received first-line therapy. For patients with a persistent response at 24 months, plots of subsequent progression-free survival after 24 months and survival after subsequent relapse (108 patients) are shown. Patients with a persistent response at 24 months (242 patients without POD24): (A) Subsequent survival (3-year estimate: 93%; 95% CI, 89%–97%). Patients with relapse or progression before 24 months (129 patients with POD24): (B) Subsequent survival (3-year estimates: 75%; 95% CI, 67%–83%). Patients with a persistent response at 24 months: (C) Subsequent progression free survival after 24 months (3-year estimate: 54%; 95% CI, 47%–61%) and (D) Survival after late (after 24 months) relapse or progression (3-year estimate: 84%; 95% CI, 77%–91%). Note: the difference in survival after progression occurring within 24 months of first treatment initiation (B) or more than 24 months after the first treatment initiation (D) was not significant ($p = 0.26$), and the hazard ratio did not change over time (data not shown)

In patients without POD24, the median subsequent PFS (i.e., after 24 months) was estimated to be 43 months (95% CI: 30–63 months, Figure 1C) and the 3-year PFS after 24 months (i.e., 5 year PFS after treatment initiation) was 54% (95% CI:47–61, Table 3). The 3 year survival rate after late progression was 84%; (95% CI: 77%–91%, Figure 1D).

3.3 | Role of baseline IPSSWM and treatment (POD24 stratified model and separate models in patients with PO24 and patients without POD24)

Multivariate Cox models of subsequent survival (after POD24 in patients with POD24 or after 24 months in patients without POD24),

stratified by POD24 showed a harmful effect of a high-risk baseline IPSSWM score (HR: 1.37; 95% CI: 1.10–1.72, $p = 0.006$) and a favorable effect of immunochemotherapy (HR: 0.6; 95% CI: 0.38–0.95, $p = 0.03$).

Table 3 showed sensitivity analyses of subsequent survival performed separately in each subgroup (patients with or without POD24). The baseline IPSSWM score had significant prognostic value in patients with POD24 but not in patients without POD24 (Table 3). The harmful effect of high-risk baseline IPSSWM score on survival after POD24, was observed regardless of first treatment received (data not shown).

There was no significant difference in subsequent survival according to first-line treatment with immunochemotherapy versus chemotherapy in patients with POD24 and patients without POD24.

TABLE 3 Subsequent survival after progression or relapse of disease before 24 months (POD24) or after 24 months in the reference (non-POD24) group, showing the role of the baseline IPSSWM score and the first-line treatment

Start date	Patient subgroup	Endpoint: Subsequent survival	Number at risk+	Number of deaths	3-year survival (95% CI)	HR (95% CI)	p Value	PHA	3-year PFS after 24 months (95% CI)
Whole series									
	POD24	After progression	129	52	75 (67–83)	ND	ND	0.036	
	Reference group	After 2 years	242	47	93 (89–97)				54 (47–61)
Patients with POD24									
	Baseline IPSSWM		110[a]	44[a]					
	Low or intermediate	After progression	59	18	86 (76–96)	1.58 (1.16–2.14)	0.0025	0.10	
	High	After progression	51	26	65 (51–79)				
	First-line treatment		140	40					
	Chemotherapy	After progression	46	31	70 (57–83)	0.58 (0.37–1.04)	0.07	0.72	
	Immunochemotherapy	After progression	83	21	78 (68–88)				
Patients without POD24									
	Baseline IPSSWM		211[a]	38[a]					
	Low or intermediate	After 2 years	122	24	93 (88–98)	1.15 (0.81–1.62)	0.42	0.5	58 (48–68)
	High	After 2 years	89	14	93 (87–99)				50 (38–62)
	First-line treatment		242	47					
	Chemotherapy	After 2 years	80	35	91 (85–97)	0.62 (0.30–1.30)	0.20	0.97	40 (30–50)[b]
	Immunochemotherapy	After 2 years	162	12	94 (90–98)				63 (54–72)[b]

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinemia; ND, not determined; PFS, progression-free survival; PHA, proportional hazards assumption.

[a]The baseline IPSSWM score for some patients was missing.

[b]The difference was significant at the 0.0003 level.

However, type of first-line treatment did improve the PFS in patients without POD24 as the 3 year PFS was 63% and 40% after chemo-immunotherapy and chemotherapy (*p* = 0.0003, Table 3), respectively.

3.4 | Prognostic analyses of survival after progression

Survival after late progression in patients without POD24 (Figure 1D) did not differ significantly from the subsequent survival in patients with PO24 (Figure 1B, *p* = 0.26, Table 4).

Regardless of the treatment received and baseline IPSSWM, the time to progression did not have significant prognostic value for survival after progression (Table 4).

4 | DISCUSSION

For the first time, we report here on the prognostic role of early progression (POD24) in sWM.

Our findings indicated that assessing the prognostic significance of POD24 (as described previously for other B-cell disorders) is difficult in sWM because of a departure from the PHA.

The reason could be, at least in part, the survival estimates starting the clock at different time (either POD24 or 24 months). Thus, this method, previously reported in other lymphoma subtypes,[7,9,10] was poorly appropriate in sWM patients, Landmark prediction model at 24 months could avoid this drawback, but it should be of limited clinical relevance, because treatment decision has to be made at the time of progression and not later at a specified time-point. Instead, dynamic predicting by landmarking could provide suitable information in sWM patients.[8] Flexible parametric survival models[18] could also be considered to take into account the violation of the proportional hazard assumption with a wide range of hazard shapes that can be captured.

Despite this limitation in the assessment of survival after POD24 or 24 months in sWM patients with POD24 or without POD24, respectively, we could demonstrate that the apparent difference between these survival estimates does not mean that POD24 is associated with an adverse prognostic value for the survival after progression. This finding, observed regardless of treatment received,

TABLE 4 Survival after first progression as a function of the time to progression [within 24 months (POD24) or after 24 months], in the patient group as a whole and in the subgroups

Study population	Time to progression	Number at risk	Number of deaths	3-year survival after progression (95% CI)	Hazard ratio for survival after progression
Whole group					
	<24 months (POD24)	129	52	75 (67–83)	1.27 (0.83–1.94) p = 0.26
	>24 months	113	38	84 (77–91)	
High IPSSWM score					
	<24 months (POD24)	51	26	65 (51–79)	1.66 (0.81–3.41) p = 0.16
	>24 months	39	11	88 (76–99)	
Low/intermediate IPSSWM score					
	<24 months (POD24)	59	18	86 (77–95)	0.95 (0.48–1.84) p = 0.87
	>24 months	52	18	89 (80–98)	
Chemotherapy					
	<24 months (POD24)	46	31	70 (57–83)	1.38 (0.84–2.29) p = 0.20
	>24 months	65	32	84 (75–93)	
Immunochemotherapy					
	<24 months (POD24)	83	21	78 (68–88)	1.63 (0.65–4.09) p = 0.29
	>24 months	48	6	86 (74–98)	

Abbreviations: IPSSWM, International Prognostics Scoring System for Waldenström macroglobulinemia; POD24, disease progression before 24 months.

is in agreement with previous reports.[6] In therapeutic trials, the time to the second treatment lacked prognostic value for subsequent outcomes in patients with sWM.[19–21] In follicular lymphoma patients, however, the marked difference in survival after POD24 or after the 24 month time point, in patients without POD24, was associated with a difference in outcome after early or late progression.[7] Hence, the prognostic significance of POD24 appears to depend on the type of B-cell disorder, and might indicate different clinical courses. In patients with follicular lymphoma, the high incidence of early histological transformation (especially after combination treatment with bendamustine and rituximab) may account for the adverse outcome after early progression.[22] In contrast, the frequencies of histological transformation in sWM in the present report and in previous studies were low and did not vary significantly over the follow-up time.[23] This is consistent with the absence of a difference in outcome between early progression and late progression.

Assessing the potential counfounding role of baseline IPSSWM, we also identified the prognostic significance of this characteristic on survival after early progression (POD24). It remains to be seen whether a baseline score calculated according to the revised IPSSWM[4] would also be significantly associated with survival after early progression. The identification of baseline molecular markers with prognostic value not only at the time when first-line therapy is initiated but also later (as reported here for the IPSSWM) should increase the accuracy of the prognosis. In view of its low frequency (5%–10%), the MYD88 wild-type phenotype will

probably not be easy to assess. Combining the MYD88 and CXCR4 mutational status as previously published (MYD88+/CXCR4− vs. MYD88+/CXCR4+ MYD88−/CXCR4−) may be more appropriate for this purpose.[5]

Regardless of the first-line treatment received, a prolonged subsequent PFS after 24 months in patients without POD24 was observed in this real-world study. It remains to be determined whether first-line therapy with ibrutinib[24] will modify these findings, once a sufficient number of events have occurred. Assessing the prognostic role of early progression in late-stage sWM will also be complex issue, given the high number of confounding factors.

In conclusion, the assessment of POD24's impact on subsequent survival (as previously reported in other B-cell lymphoid disorders) is difficult to apply to patients with sWM because of departure from the PHA. The prolonged subsequent survival of patients without POD24 is likely explained by their prolonged subsequent PFS after 24 months. Indeed, survival after progression in patients with sWM is not influenced by the time to progression, regardless of the treatment received.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare with regard to this study.

AUTHOR CONTRIBUTIONS

Julien Labreuche and Pierre Morel designed the study; Deborah Assouan, Eric Durot, Cecile Tomowiak, Damien Roos-Weil, Elise Toussaint, Fontanet Bijou, Richard Lemal, Annie Brion, Kamel Laribi, Loic Ysebaert and Pierre Morel collected the patients' clinical data; Julien Labreuche, Alain Duhamel and Pierre Morel performed statistical analyses; Julien Labreuche, Deborah Assouan, Alain Duhamel and Pierre Morel wrote the manuscript. All authors approved the manuscript as submitted.

DATA AVAILABILITY STATEMENT

Data presented in this study are available in the Article or available from the corresponding author upon reasonable request.

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PEER REVIEW

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