Impact of initial FGD-PET CT and Serum Free Light Chain on transformation of conventionally defined Solitary Plasmacytoma to Multiple Myeloma

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Statement of translational relevance

There is growing evidence that certain malignant gammopathies with high risk to transformation within 2 to 5 years to overt myeloma should be treated earlier, such as smoldering myeloma. We have identified a subgroup of solitary plasmacytoma that display a greater risk to evolve towards overt myeloma within 2 years, as compared to a group likely to be cured using the current recommended treatment. The predictors of early evolution to myeloma are an abnormal involved sFLC value and the presence of at least two hypermetabolic lesions on PET/CT at diagnosis in our series. This data analysis may lead to a different management of solitary plasmacytoma irrespective to its solitary clinical presentation. One may consider to embrace treatment of myeloma for solitary plasmacytoma when FDG-PET CT and involved sFLC value are abnormal at diagnosis, while surgery and/or radiotherapy would remain the appropriate therapeutic procedure for solitary plasmacytoma otherwise.

Abstract

Purpose. Solitary plasmacytoma (SP) is a localized proliferation of monoclonal plasma cells in either bone or soft tissue, without evidence of Multiple Myeloma (MM), and whose prognostic is marked by a high risk of transformation to MM.

Experimental design. We studied the impact of FDG-PET/CT on the risk of transformation of SP to overt MM amongst other markers in a series of 43 patients diagnosed with SP.

Results. Median age was 57.5 years, 48% patients had abnormal involved sFLC value and 64% abnormal sFLC ratio at diagnosis. 33% had ≥2 hypermetabolic lesions on initial PET/CT, and 20% had ≥2 focal lesions on initial MRI. With a median follow-up of 50 months, 14 patients transformed to MM with a median time (TTMM) of 71 months. The risk factors that significantly shortened TTMM at diagnosis were ≥2 hypermetabolic lesion on PET/CT and abnormal sFLC ratio and involved sFLC; and in a lesser extent at completion of treatment, absence of normalized involved sFLC and PET/CT or MRI. In multivariate analysis, abnormal initial involved sFLC (OR=10, 95%CI=1-87; p=0.008) and PET CT (OR=5, 95%CI=0-9; p=0.032) independently shortened TTMM.

Conclusion. An abnormal involved sFLC value and the presence of at least two hypermetabolic lesions on PET/CT at diagnosis of SP were the 2 predictors of early evolution to myeloma in our series. This data analysis will need confirmation in a larger study, and the study of these 2 risk factors may lead to a different management of patients with SP in the future.

Introduction

Solitary plasmacytoma (SP) is a rare plasma cell neoplasia characterized by a localized proliferation of monoclonal plasma cells resulting in a tumor, without evidence of either bone-marrow plasma-cell infiltration or systemic plasma-cell proliferative disorder, e.g. absence of evidence of Multiple Myeloma (MM) [1-4]. SP can be localized in either bone (SBP for Solitary Bone Plasmacytoma) or soft tissue (EMP for Extra-Medullary Plasmacytoma, usually located on the head and neck, and especially in the nasal cavity and nasopharynx) [1]. Multiple solitary plasmacytoma can be observed in up to 5% of patients. The prognosis of SP is essentially marked by a high risk of transformation to MM, which occurs in almost 50% of patients with SBP [4], 15% of patients with EMP [5], and can happen up to 15 years after diagnosis. Historical prognosis factors for progression to MM are SBP (compared with EMP), older age, tumor size > 5 cm [6], and persistence of monoclonal immunoglobulin at completion of treatment [7].

The presence of focal lesions on magnetic resonance imaging (MRI) is an important prognostic factor in MM [8], particularly in Smoldering Multiple Myeloma [9], including those with plasmacytoma [10]. Recent studies showed that FDG-PET CT (Fluorodeoxyglucose Positron Emission Tomography – Computed Tomography) provides additional valuable information for the assessment of MM compared with MRI [11], especially when presence of plasmacytoma [12, 13]. The prognostic role of PET CT has not been formally determined in SP, nor has its role been studied in reassessment of diagnosis from SP to multiple solitary plasmacytoma.

We aimed to determine the impact of FDG-PET CT in the management of SP, for the evaluation of the risk of progression to MM.

Materials and Methods

Patients. We retrospectively reviewed the medical records of 43 patients from three French centers (Lille, Caen and Rennes) of the IFM (Intergroupe Francophone du Myélome), diagnosed from 2002 to 2013 with a solitary plasmacytoma.

All patients had clinical evidence of a solitary plasmacytoma, either EMP (10 patients) or SBP (33 patients). The diagnosis of plasmacytoma was confirmed by histological evidence of a tumor made of

a proliferation of monoclonal plasma cells, as described in guidelines. The initial evaluation of SP ensured the absence of criteria for MM, especially a bone marrow not consistent with MM (< 10% plasma cells) and no end organ damage or tissue impairment defined by the absence of the CRAB criteria (hypercalcemia, renal insufficiency, anemia, or bone lesions using standard whole body X-rays other than solitary bone lesion in the case of SBP) [4]. Treatment of SP consisted in surgery when possible (especially for EMP) and/or radiotherapy, from 30 to 50 Grays in our study.

The study was approved by the ethics committee of CHRU of Lille, and was conducted in accordance with the principles of the Declaration of Helsinki.

Assessment. Whole body PET CT and MRI of the spine and pelvis were performed at diagnosis prior to (initial) and at completion of therapy (3 months to 1 year after the end of treatment). Serum free light chains were assessed by the value of involved serum Free Light Chain (isFLC) and by the κ/λ ratio (abnormal if <0,26 or >1,65). All patients had completed follow up records pre and post therapy. When hypermetabolic lesions were identified on PET CT, standard X rays were always performed if possible ; however, we have relied on the CT part of the PET CT most of the time to identify presence or absence of underlying osteolytic bone lesions.

Statistics. Descriptive data were collected for the cohort. All survival end points were evaluated through the Kaplan-Meier estimates and compared through the Log-rank test. The relative risk of event and its 95% confidence interval (95%CI) were estimated through proportional hazard model. Univariate and multivariate analysis were performed. We constructed a 4 categories model based on 2 variables, isFLC and PET CT at diagnosis, the 2 independent variables that impacted TTMM using multivariate analysis. The categories that didn't show any statistical difference for the study of the TTMM end point were regrouped, that is to say, the 2 categories characterized with either "at least two hypermetabolic lesions" on PET CT or "abnormal involved sFLC" were regrouped. The subsequent prognostic model was thus simplified to a final model with 3 categories. All analyses were done with the SPSS 15.0 software.

Results.

Characteristics of patients.

Table 1 summarizes the characteristics of the patients. The median age was 57,5 years, with 33% patients older than 65 years. The sex ratio was 1,8. 18 (42%), 21 (49%), 11 (26%), and 24 (56%) patients had a measurable disease, using serum protein electrophoresis or SPEP (serum and/or urine), involved sFLC, sFLC ratio, and immunofixation (serum and/or urine), respectively. IgG kappa was the most frequent isotype, and the higher M-spike value was 30g/L. While all studied patients had a unique clinical evidence of SP, we noticed that 10 (23%) had at least 2 hypermetabolic lesions on initial PET CT, and 7 (16%) had at least 2 focal lesions on initial MRI. The median number of either hypermetabolic lesions or focal lesions on the initial PET CT or MRI, respectively, was 2 (median 1, range min-max 1-3). The other hypermetabolic lesions or focal lesions did not correspond to osteolytic lesion or any other soft tumor mass, as assessed by standard X-rays and by the CT part of the TEP/CT. Out of the SBP, 17 (51%) were localized on spine or pelvis.

15 patients (34,8%) developed a MM in our series and 5 patients (11,6%) died during follow-up. Amongst the 10 patients with at least 2 hypermetabolic lesions on initial PET CT, 6 patients progressed to MM. Similarly, amongst the 7 patients with at least 2 focal lesions on MRI at diagnosis, 4 patients progressed to MM. 15 patients had an abnormal involved sFLC at diagnosis, amongst whom 9 patients developed a MM.

Shorter TTMM correlated with initial PET CT and isFLC value.

With a median follow-up of 50 months, the median time to MM progression (TTMM) was 71 months for the whole cohort (95%CI: 59;101). We found no significant difference of TTMM between SBP and EMP, although the 5-year TTMM was 45% and 83%, respectively (Table 2).

Using univariate analysis, we found that sFLC but not SPEP M-spike or immunofixation, and PET CT but not MRI, influenced TTMM (Table 2). The TTMM for the group with at least 2 hypermetabolic lesions on initial PET CT was 23 months (9;37) versus not reached otherwise (p=0.003) (Figure, panel A). Conversely, MRI at diagnosis did not have any impact on TTMM in our study, although the median TTMM for the group with at least 2 focal lesions on initial MRI was lower, 30 months (9;51) versus not reached otherwise (p=ns). We also observed that abnormal initial κ/λ ratio (p=0.022) and abnormal initial isFLC value (p=0.002) did impact TTMM, 36 months (14;58) and 21 months (0;42) versus not reached otherwise, respectively (Figure, panel B).

Surprisingly, a normalized PET CT (defined by the absence of remaining hypermetabolic lesion on the main plasmacytoma that required therapy**)** at completion of treatment did not reach significance, as to a normalized MRI (similar definition), but the absence of normalized isFLC value also impacted TTMM, 21 months (10;32) versus not reached otherwise (p=0.016).

Using multivariate analysis, initial isFLC value (OR=10, 95%CI=1-87; p=0.008) and initial PET CT (OR=5, 95%CI=0-9; p=0.032) were the strongest independent prognostic factors that impacted TTMM. Based on these results, we proposed a model of 4 categories with these 2 variables. The most adverse categories regarding TTMM included patients with abnormal initial isFLC value and at least 2 hypermetabolic lesions on initial PET CT (PET $\geq$ 2) (with all but one patient that developed overt MM), while the group with normal initial isFLC value and less than 2 hypermetabolic lesions on initial PET CT (PET < 2) displayed the best prognostic (with none of the patients that developed overt MM). The remaining 2 categories with abnormal initial isFLC and PET < 2 or with normal initial isFLC and PET $\geq$ 2 had an intermediate prognostic, with no statistical significant difference between the 2 groups. We thus regrouped these 2 categories to create a simplified 3 categories with 2 variables model. Using this latter model we have been able to separate the 3 groups with median (+/-se) TTMM of 21 (+/-2) months for the worse category [5 patients, including 4 (80%) that developed MM], 41 (+/-2) months for the intermediate category [24 patients, amongst whom 11 patients (45,8%) developed a MM], and finally median TTMM not reached for the best category [14 patients, none developed a MM] (p=0.004 and 0.002, respectively) (Table 3 and Figure, panel C).

With a special focus on SBP, we identified the exact same prognostic factors for TTMM as for the whole cohort, in univariate and multivariate analysis. The localization of SBP in the spine is usually considered of poor prognosis, but we did not find any confirmation of this observation in our study.

Shorter TTMM is not associated with shorter OS in our series.

The median overall survival (OS) was not reached for the whole cohort, with a 6-year OS at 79.4%. Although the median OS of patients with SP from start of MM was not reached, similar to SP that did not progressed towards MM, the 4-year OS was 66% compared to 92% (p=ns). This difference did not appear statistically shorter, but that might be related to the limited number of patients recruited in the study. Interestingly, initial PET CT did not seem to influence OS, with a median of 71 months for the

"PET ≥ 2" group versus not reached otherwise, respectively (p=ns). Similar observation was obtained with isFLC value.

The presence of SP at time of MM diagnosis is usually considered of adverse prognostic for OS. Interestingly, when considering the prolonged OS of patients with SP that transformed later on to MM, and compared with de novo MM in the literature, we could extrapolate that SP that transformed to MM were not of worst prognostic compared to newly diagnosed myeloma with no features of adverse prognostic. It seems that the SP that transformed towards MM could appropriately be rescued by the current therapeutic approach of myeloma.

Discussion

Since the major issue in the management of solitary plasmacytoma lies in its inherent risk of transformation to multiple myeloma, initial assessment should be focused on the detection of asymptomatic lesions in order to ensure that the patient does not already have a widespread disease that would require a systemic treatment or, more importantly, an occult lesion from which multiple myeloma would develop and spread over the whole body bone marrow. Biological factors at diagnosis of SP have been associated to the risk of development of MM, mainly markers of the M-spike component as an assessment of the initial tumor burden. There has always been a great need for iconography to identify these occult lesions, and the introduction of MRI was an important breakthrough compared to the historical use of skeletal X-rays, CT scanner and scintigraphy ; however, the question of the best imaging technique for the detection of these occult lesions is not yet fully resolved.

In this study, we found that the presence of at least two hypermetabolic lesions detected by FDG-PET CT was an important risk factor for progression to MM, compared with none or only one hypermetabolic lesion. This suggest that the diagnosis of SP should not be solely based on clinic, but should integrate sensitive imagery techniques. We believe, although we acknowledge that it is a matter of debate still, that PET CT is one of them, possibly similar to whole body MRI. This could imply that patients with multiple pathological lesions, even if no proof of a widespread disease is found, could already present an early stage of MM and be at risk of transformation when treated only locally. In that

setting, the identification of multiple hypermetabolic signals, even though not clinically relevant in the context of SP, should modify the diagnosis to multiple solitary plasmacytoma and thus make consider systemic treatment as to MM treatment approach [14].

PET CT was rarely investigated in Smoldering Multiple Myeloma (SMM) and SP, and seemed a very promising technique, but its value is not well recognized yet [15]. Warsame and al. found that the association of a negative PET CT and a negative bone marrow (but not a negative PET CT alone) had a good predictive value for a lower likelihood of progression to MM, in a retrospective series of 127 SBP at Mayo Clinic [16] ; an abnormal initial κ/λ ratio was also a poor prognostic factor for progression to MM. Kim and al. confirmed FDG-PET CT as a useful technique for initial staging of SP, and also for response assessment after radiotherapy [17]. This findings are consistent with those found in related plasma cell diseases, such as MGUS and SMM. Durie and al. also showed that the presence of extramedullary hypermetabolic lesions on PET CT was a poor prognostic factor either at start of treatment or at relapse, in a series of 66 patients with MM at different stages of the disease [18]. Furthermore, a persistent abnormal FDG uptake after treatment was predictive of relapse.

The impact of MRI was not significant in our series, but patients with at least 2 focal lesions or seemed to be at higher risk of progression than the others. Few studies have shown that abnormal MRI can impact the progression to MM for SMM [9] and SP [10]. MRI was thus considered a major imagery technique for the initial staging of SP, able to detect asymptomatic lesions that would orientate the diagnosis towards MM with presence of plasmacytoma rather than SP [10].

Recent studies have found that FDG-PET CT provides additional valuable information for the assessment of MM compared with MRI [11]. Salaun and al. compared the value of MRI and FDG-PET CT for SP in a series of 24 patients at diagnosis for initial staging, and after treatment [12]. They found that PET is equivalent to MRI for evaluation of spine and pelvis, but that it allowed a better evaluation of soft tissues, skull, ribs and limbs. They also concluded that PET CT showed a higher performance than MRI for therapeutic assessment.

Oddly, the correction of PET CT lesions after treatment (defined by the absence of remaining hypermetabolic lesion on the main plasmacytoma that required therapy**)** was not significantly associated with a longer TTMM, neither did the correction of MRI lesions. However, as there is a lack

of recommendations for the use of PET CT in SP, the ideal time for post treatment assessment is not defined and several patients had a PET CT quickly after treatment in our study. The persistence of abnormal FDG uptake could have been distorted by recent treatments, especially after radiotherapy.

Interestingly, in our series, the presence of at least 2 hypermetabolic lesions detected by PET CT impacted the time to MM progression, but not the overall survival. Although our data seem to say that patients who developed MM later on after diagnosis of SP did not seem to have a poorer prognostic at time of MM than patients with *de novo* MM with no adverse features in the same age group, the 4-year OS was shorter in these patients compared to SP that did not progress to MM. This data should be confirmed in a larger study.

The concerns over identifying and treating plasma cell malignancies earlier in the malignant process development have never been as present as nowadays, with the recent understanding that clonal evolution occurs very early in malignant plasma cells. One would hope that early treatment of SP could give the patient a chance to cure, while this cure cannot be obtained after progression to MM, as it is considered a very complex genomic cancer at the time of transformation [19].

The identification of sub groups of SMM and SP with a greater risk to develop overt MM (possibly renamed as Early MM in the near future, at least for the high risk SMM) in a short period of time, is of importance and relevance to the field and to the patients. A study recently demonstrated that high risk SMM appeared to highly benefit from early treatment approach in terms of prolonged TTMM and more importantly OS, rather than to wait for development of symptomatic MM to start treatment [20]. The definition of Early MM remains debatable, and whether all currently defined high risk SMM are early MM remains however an important matter of debate [21]. Similarly, an early treatment for SP should only be proposed to patients identified as being at higher risk, through well-defined prognostic risk factors. It must be proven at least equivalent to local treatment in terms of response, and superior with regard to PFS, or even OS. Finally, it must have an acceptable toxicity profile in order to avoid side effects related to a possibly unnecessary treatment, and preserve the patient's quality of life. FDG-PET CT and involved sFLC value are important predictors of the risk of progression from SP to MM in our study. PET CT appears to be a sensitive technique to help reveal multiple hypermetabolic lesions, beyond the clinical SP presentation, that should encourage experts to revise the diagnosis of

SP and possibly rename this as multiple solitary plasmacytoma – corresponding to Early myeloma since early systemic MM treatment approach is recommended [14].

This data analysis may lead to a different management of SP for patients with one or both of these 2 abnormal indicators, irrespective to the solitary clinical aspect of SP. One may consider to embrace systemic treatment (that is to say, to treat as MM) when FDG-PET CT shows at least two hypermetabolic lesions and when the involved sFLC value is abnormal at diagnosis of SP, both predictors of early evolution to myeloma in our series. Surgery and/or radiotherapy would remain the appropriate therapeutic procedure for SP otherwise.

Conclusion

FDG-PET CT and involved sFLC at diagnosis of SP are important predictors of the risk of progression to MM. Further studies are needed in order to confirm these factors, to consider developing a risk stratification model at diagnosis of SP, and then to determine whether a group of SP at high risk could benefit from an early systemic treatment rather than a local treatment, before transformation to multiple myeloma.

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Contribution of authors.

Conception and design: GF, DH, and XL

Collection and assembly of data: GF, SG, CH, ZVW, SB, DB, HD, BH, MW, CB, LT, VC, MM, OD, TF, and XL

Data analysis and interpretation: GF, DH, SA and XL

Manuscript writing: GF and XL

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Table 1. Characteristics of patients at entry into the study (at diagnostic) (N=43)

		Overall cohort	SBP
		N (%)	N (%)
Gender	**Men**	28 (65)	22 (67)
	Women	15 (35)	11 (33)
Localization	**Bone (SPB)**	33 (77)	-
	Soft tissues (EMP)	10 (23)	-
Isotype	**IgG**	18 (42)	16 (48)
	IgA	5 (12)	5 (15)
	No M spike	24 (56)	16 (48)
	Light chain only	20 (46)	12 (36)
sFLC	**Kappa**	24 (56)	17 (51)
	Lambda	15 (35)	14 (42)
	Abnormal ratio	11 (26)	10 (30)
	Abnormal Involved	21 (49)	15 (45)
MRI	**≥ 2 focal lesions**	7 (16)	6 (18)
FDG-PET CT	**≥ 2 hypermetabolic lesions**	10 (23)	9 (27)

SBP. Solitary Bone Plasmacytoma; EMP. Extra-Medullary Plasmacytoma; sFLC. Serum free light chain; MRI. magnetic resonance imaging; FDG-PET CT. Fluorodeoxyglucose Positron emission tomography - computed tomography

Table 2. Impact of biological test and medical imaging factors on time to multiple myeloma progression (TTMM, N=43)

		Median TTMM	(CI 95%)	p
At diagnosis				
Localization	**SPB**	23 months	(25-116)	ns
	EMP	Not reached	-	
PET CT (hypermetabolic lesions)	**< 2**	Not reached	-	0,003
	≥ 2	23 months	(9;37)	
MRI (focal lesions)	**< 2**	Not reached	-	ns
	≥ 2	30 months	(9;51)	
isFLC value	**Normal**	Not reached	-	0,002
	Abnormal	21 months	(0;42)	
κ/λ ratio	**Normal**	Not reached	-	0,022
	Abnormal	36 months	(14;58)	
At completion of treatment				
PET CT	**Normalized**	Not reached	-	ns
	Not normalized	60 months	(25;95)	
MRI	**Normalized**	Not reached	-	ns
	Not normalized	Not reached	-	
isFLC value	**Normalized**	Not reached	-	0.016
	Not normalized	21 months	(10;32)	

PET CT. Positron emission tomography - computed tomography; MRI. magnetic resonance imaging; isFLC. Involved serum Free Light Chain

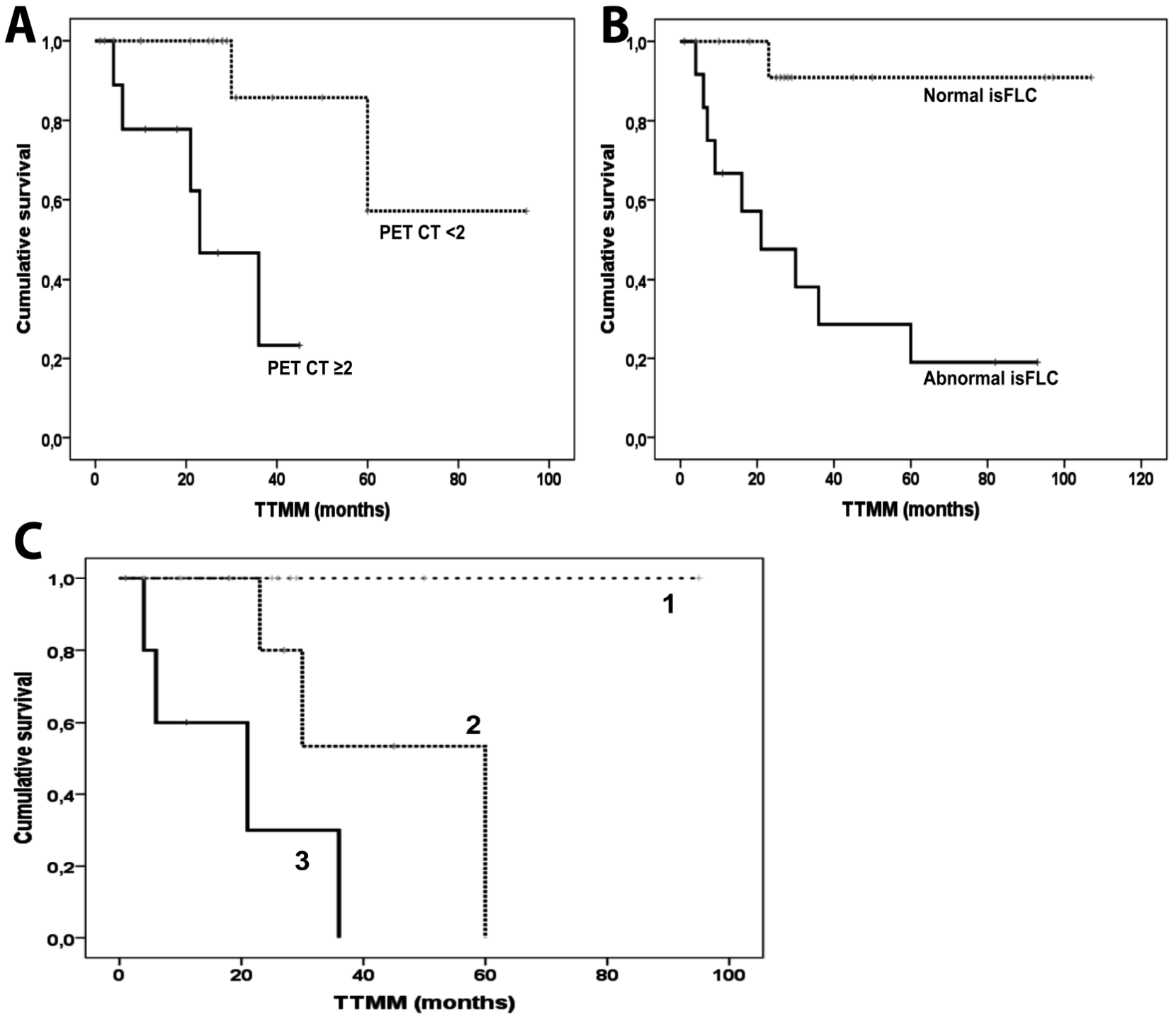
Table 3. Proposed risk model for progression from solitary plasmacytoma to multiple myeloma, with 2 variables and 3 categories.

1) represents the group with normal isFLC and less than 2 hypermetabolic lesions on initial PET CT; 2) represents the group with either abnormal isFLC value and less than 2 hypermetabolic lesions on initial PET CT or normal isFLC value and greater or equal 2 hypermetabolic lesions on initial PET CT; and 3) represents the group of patients with abnormal initial isFLC value and greater or equal 2 hypermetabolic lesions on initial PET CT. m: months. Se: standard event. HR: relative risk of event. 95%CI: 95% confidence interval. P: significance. se Standard event.

	Categories	TTMM Median (m; +/- se)	HR (95% CI)	p
1	**Normal isFLC + PET CT < 2**	Nr	-	-
2	**Abnormal isFLC + PET CT < 2 or Normal isFLC + PET CT ≥ 2**	41 (2)	5 (0;16)	0,002
3	**Abnormal isFLC + PET CT ≥ 2**	21 (2)	25 (0;76)	0,004

Figure. Time to progression towards MM according to isFLC and PET CT at diagnosis of SP. **A**. Based on greater or equal 2 hypermetabolic lesions on initial PET CT versus less than 2 lesions. **B**. Based on normal versus abnormal isFLC value. **C**. Risk model with 2 variables and 3 categories (Table 3). 1) represents the group with normal isFLC and less than 2 hypermetabolic lesions on initial PET CT; 2) represents the group with either abnormal isFLC value and less than 2 hypermetabolic lesions on initial PET CT or normal isFLC value and greater or equal 2 hypermetabolic lesions on initial PET CT; and 3) represents the group of patients with abnormal initial isFLC value and greater or equal 2 hypermetabolic lesions on initial PET CT.

Figure.



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