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The Nanocind Signature Is an Independent Prognosticator of Recurrence and Death in Uterine Leiomyosarcomas

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ABSTRACT

Purpose: Uterine leiomyosarcoma, which accounts for 7% of all soft-tissue sarcomas and 1%–3% of all uterine malignancies, is an aggressive tumor responsible for a significant proportion of uterine cancer–related deaths. While Federation Internationale des Gynaecologistes et Obstetristes (FIGO) stage is the most important prognostic factor, metastatic and relapse rates at stage I exceed 50% so it is currently impossible to predict the clinical outcome of stage I leiomyosarcomas. In 2010, our team published a transcriptomic signature composed of 67 genes related to chromosome biogenesis, mitosis control, and chromosome segregation. It has demonstrated its prognostic value in many cancer types and was recently successfully applied to formalin-fixed, paraffin-embedded sarcomas by NanoCind on NanoString technology, making another step forward toward its use in routine practice.

Experimental Design: Sixty uterine leiomyosarcomas at any stage, including 40 localized in the uterus (stage I), were analyzed with the NanoCind (CINSARC with NanoString) signature. Its prognostic value was evaluated for overall survival and relapse-free survival and compared in multivariate analysis with other prognostic markers like FIGO staging and genomic index.

Results: The NanoCind signature was able to split the heterogeneous group of uterine leiomyosarcomas of any stage including stage I into two distinct groups with different relapse-free survival and overall survival. These results were validated on an independent cohort of uterine leiomyosarcomas in The Cancer Genome Atlas consortium.

Conclusions: The NanoCind signature is a powerful prognosticator that outperforms FIGO staging and the genomic index. The CINSARC signature is platform independent and "ready to use" and should now be used for randomization in future therapeutic trials.

Introduction

Uterine leiomyosarcoma is a rare tumor accounting for 7% of all soft-tissue sarcomas (STS; refs. 1, 2) and 1%–3% of uterine malignancies (3, 4), but it is the most frequent subtype representing 57%–60% of all uterine sarcomas (4). Owing to its aggressiveness, 5-year overall survival (OS) is 41% for all stages (5), 51% at stage I, 25% at stage II, and no survival at 5 years in patients with tumor spread outside the pelvis (4). Furthermore, uterine leiomyosarcoma accounts for a significant proportion of uterine cancer–related deaths (3, 4) with an annual incidence estimated between 0.36 (1) and 0.8 (6) per 100,000 women-year and 0.5 to two per 100,000 women-year in the age group 35–64 years (7).

Among the prognostic factors, FIGO stage is still the most important prognosticator in uterine leiomyosarcoma and guides the therapeutic strategy (8–10). Because most uterine leiomyosarcoma are diagnosed at stage I (4, 5), that is, confined to the uterus, it is impossible to distinguish the patients who will recur and die of the tumor from those with a long survival. A specific uterine leiomyosarcoma nomogram for predicting postresection 5-year OS was published recently (11, 12). The items of the nomogram are based on clinicopathologic parameters such as age, tumor size, tumor grade, cervical involvement, loco regional metastases, distant metastases, and mitotic index (11). One of its limitations is the value of tumor grade, as there is no recognized tumor grade according to the 2014 World Health Organization (WHO) classification of the gynecologic and reproductive organs (13), and uterine leiomyosarcoma diagnosed according to the Stanford criteria (14) are by definition of high grade (15).

As stated by Pautier and colleagues on a series of 157 uterine sarcomas, the Fédération Nationale des Centres de Lutte Contre le Cancer (FNLCC) grading score could not be used as a prognostic indicator for uterine leiomyosarcoma (16).

The analysis of chromosome complexity in uterine leiomyosarcoma by comparative genomic hybridization (CGH) array recently demonstrated the prognostic value of the genomic index (GI) at the cutoff of

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Uterine leiomyosarcoma is one of the most aggressive uterine cancers with a risk of recurrence superior to 50% at stage I. Despite the high risk of recurrence there is not an evidence of benefit of adjuvant treatment. We are convinced that to demonstrate a benefit from the new drugs in early stage uterine leiomyosarcoma we need to find the pertinent tools of randomization. In this study, we demonstrated for the first time the strong prognostic value of CINSARC NanoCind signature in uterine leiomyosarcoma outperforming the stage. The feasibility and robustness of CINSARC NanoCind signature was recently demonstrated on formalin-fixed, paraffin-embedded sarcomas, even on biopsy material. Our data were validated on an external series of uterine leiomyosarcoma published on The Cancer Genome Atlas. CINSARC NanoCind signature could be a useful and pertinent tool of randomization in the future clinical trials evaluating the benefit of adjuvant treatment on uterine leiomyosarcoma, in particular at early stage.

35 for OS but not relapse-free survival (RFS; ref. 17). In 2010, our team published a prognostic transcriptomic signature obtained by a combination of differentially expressed genes in FNLCC grade 3 versus one and two STS, and in highly rearranged tumors versus those with a low level of chromosome rearrangements and complexity (18). This 67-gene signature composed of genes belonging to significantly enriched pathways related to chromosome biogenesis, mitosis control, and chromosome segregation (18, 19) has demonstrated its prognostic value in 21 of 39 cancer types, outperforming more than 15,000 different signatures (20). Recently, the CINSARC signature was successfully applied to formalin-fixed, paraffin-embedded (FFPE) sarcomas by NanoCind, a NanoString Technology, with a similar risk-group classification on frozen, as well as FFPE tumor, and even on biopsy material (21). Given the limitations of prognostication devices currently applied or foreseen for uterine leiomyosarcoma, we tested whether the NanoCind prognostic signature could improve prognostication in uterine sarcomas.

Materials and Methods

Tumor samples

The series of 56 uterine leiomyosarcoma and five Smooth muscle Tumors of Uncertain Malignant Potential (STUMP), centrally reviewed and diagnosed according to Stanford criteria (13–15), were classified in 61 uterine leiomyosarcoma after GI analysis at a cutoff of 10, as reported previously (17, 22). Follow-up and clinical data were obtained for each case.

The samples from the tumor archives were centralized in the Biological Resources Center of Institut Bergonié, which the French authorities authorized for scientific research (AC-2008-812).

Clinical data

Among the 60 interpretable uterine leiomyosarcoma (one sample not interpretable for CINSARC/NanoCind analysis), 40 (67%) were at stage I, (six at stage IA, 30 at stage IB, and 4 at stage I without other specification), three (5%) at stage II, six (10%) at stage III, nine (15%) at stage IV, and for two (3%) the stage was not known.

Regarding the modalities of surgery, it was not possible to specify whether any of the patients included in the study had morcellation procedure for resection of the tumor.

At follow-up, only 12 patients (20%) were alive without evidence of disease (mean, 6.66 years; median, 6.5 years; minimum, 2.2 years; maximum, 9.7 years). Among them, two had a peritoneal relapse at 35 months and a lung metastasis at 4.5 months after the first surgery but were alive without evidence of disease at last control. Nine of 60 (15%) were alive with evidence of disease at last follow-up (mean, 7.3 years; median, 6.4 years; minimum, 3.2 years; maximum, 12.6 years) and 39 of 60 (65%) had died of disease (mean, 3.2 years; median, 2.4 years; minimum, 0.2 years; maximum, 19.7 years).

CGH analysis

DNA extraction and CGH array from 45 uterine leiomyosarcomas and five STUMPs published before (17), as well 11 new uterine leiomyosarcoma were performed as described previously (17, 22).

NanoCind signature

RNA extraction and the analysis on the nCounter code set (NanoCind, patent number EP18305190·3; panel of 75 probes targeting 67 distinct CINSARC genes and eight housekeeping genes) were performed as described previously (21).

Results

Clinicopathologic, genomic, and transcriptomic data are presented in Supplementary Table S1. We carried out the CINSARC signature analysis on the series composed of 61 genomic uterine leiomyosarcomas of all stages. All, but one, were interpretable (final series: 60 uterine leiomyosarcomas).

CINSARC NanoCind signature predicts uterine leiomyosarcoma patients' outcome

The CINSARC signature split the heterogeneous population of uterine leiomyosarcoma at any stage into a group with high risk of relapse and metastases [RFS; $P = 6.7 \times 10^{-4}$; HR = 3.71 (1·65–8·32); **Fig. 1A**] as well as shorter OS [OS; $P = 7.56 \times 10^{-4}$; HR = 5.97 (1·83–19·48); **Fig. 1B**] and a group with long survival and lower risk of recurrence (**Table 1**). We thus compared the prognostic value of CINSARC to that of GI. Among the 60 tumors of the series (previously reported, refs. 17, 22), one was not analyzed by CGH array because there was not enough material and three were not interpretable. All the 56 interpretable tumors had a GI > 10 (genomic uterine leiomyosarcoma; from 11 to 180).

By applying a cutoff of 35 as defined previously (17), GI was prognostic for OS at all stages [OS; $P = 1.48 \times 10^{-2}$; HR = 2.39 (1.16–4.91); **Fig. 1C**] and at stage I (OS; $P = 6.9 \times 10^{-3}$; HR = 4.16 (1.36–12.74); **Fig. 2C**] but not for RFS ($P = 6.03 \times 10^{-1}$). Multivariate analysis showed that the CINSARC NanoCind signature outperformed GI by CGH array because the prognostic value of GI was no longer significant for OS (CINSARC: $P = 1.91 \times 10^{-3}$, HR = 4.41 (1.64–16.43); GI: $P = 9.03 \times 10^{-2}$, HR = 1.84 (0.91–3.96)]. RFS was not tested because GI was not significant at univariate analysis.

CINSARC NanoCind signature predicts stage I FIGO uterine leiomyosarcoma patients' outcome

Even if no clinical or histologic criteria can discriminate poor prognosis patients within FIGO stage I tumors (localized and accordingly considered as patients with good prognosis), the CINSARC signature showed its prognostic value for these stage I uterine leiomyosarcoma by identifying patients with low RFS [$P = 3.38 \times 10^{-3}$; HR = 3.83 (1.46–10.08); **Fig. 2A**] and OS (OS; $P = 9.89 \times 10^{-3}$; HR = 5.51 (1.28–23.69); **Fig. 2B**]. Indeed, among the 27 of 40 (67.5%) stage I

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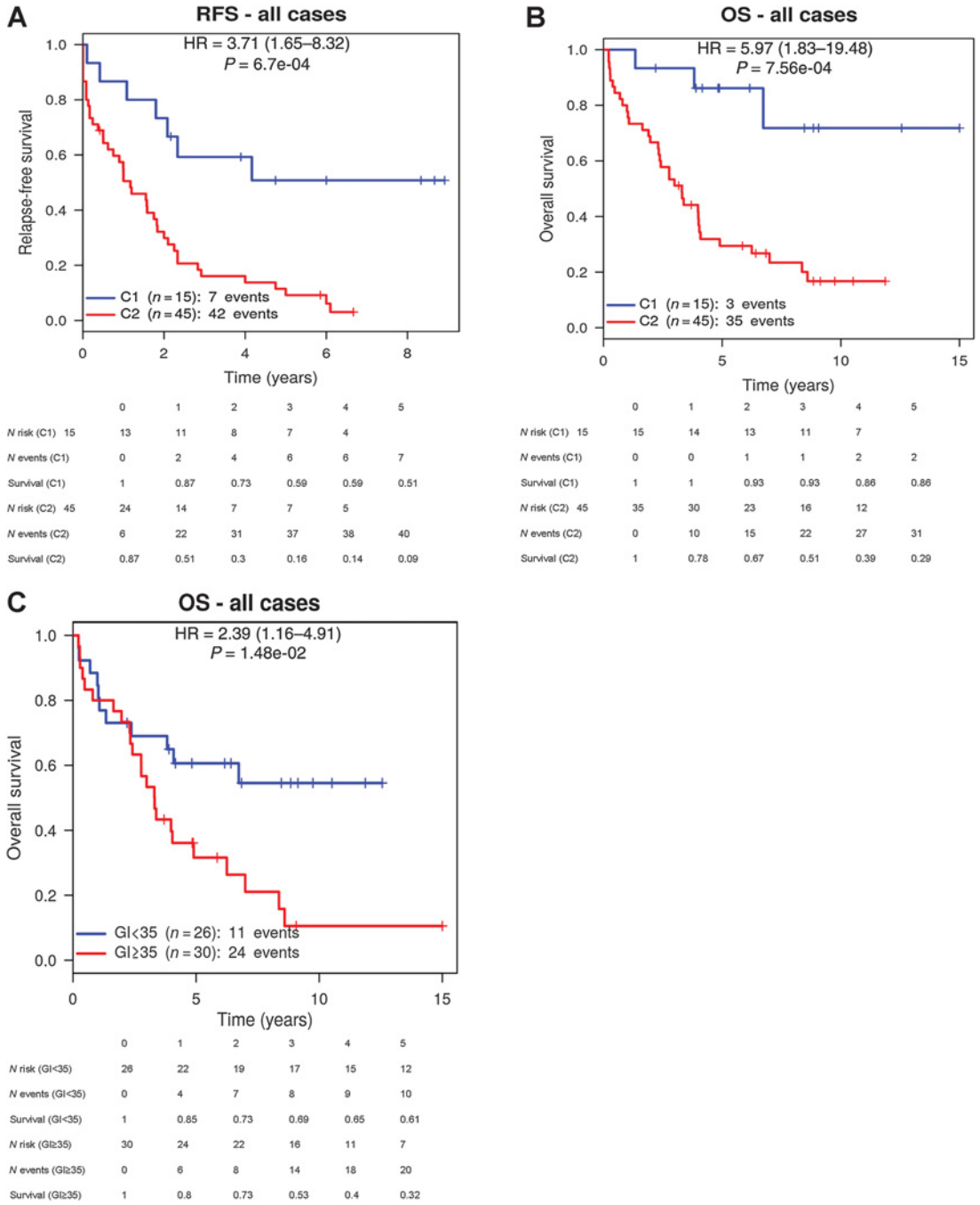

Figure 1.

RFS (**A**) and OS (**B**) analysis according to CINSARC signature for uterine leiomyosarcomas at any stage. **C,** OS analysis according to GI at the cutoff of 35 for any stage uterine leiomyosarcoma.

uterine leiomyosarcoma classified by the signature as having a high risk of recurrence and death (C2, for centroid 2), 85% had a dismal outcome: 19 of 27 (70.3%) died of disease and four of 27 (14.7%) were alive with disease (Supplementary Table S1). On the other hand, among the 13 (32.5%) uterine leiomyosarcoma at stage I classified as low risk (C1, for centroid 1), eight of 13 (62%) were alive without evidence of disease, two of 13 (15%) alive with disease, and three of 13 (23%) had died of disease.

At morphologic analysis, the C2 (high-risk) group of uterine leiomyosarcoma had a higher mitotic count ($P = 3.5 \times 10^{-7}$; Wilcoxon test), and more frequently harbored tumor cell necrosis ($P = 0.036$; Fisher exact test) compared with C1 patients (low-risk group). No statistically significant difference was observed between the C1 and C2 groups for the presence of atypia ($P = 0.6$; χ^2 test). At univariate analysis, the presence of atypia was correlated with low survival (OS: $P = 4.27 \times 10^{-2}$; HR = 2.03 (1·01–4·12)] but not with

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Table 1. Prognostic analysis of the cohort.

Total patients	61	DOD	AWD	NED	OS	HR (95% CI)	RFS	HR (95% CI)
CINSARC NanoCind interpretable	60							
All stages	60							
C1	15	4	3	8	$P = 7.56 \times 10^{-4}$	5.97 (1.83–19.48)	$P = 6.7 \times 10^{-4}$	3.71 (1.65–8.32)
C2	45	35	6	4				
Stage I	40							
C1	13	3	2	8	$P = 9.89 \times 10^{-3}$	5.51 (1.28–23.69)	$P = 3.38 \times 10^{-3}$	3.83 (1.46–10.08)
C2	27	19	4	4				
Array-CGH interpretable	56							
All stages	56							
≤35	21	8	6	7	$P = 1.48 \times 10^{-2}$	2.39 (1.6–4.91)	$P = 6.03 \times 10^{-1}$	
≥35	35	28	2	5				
Stage I	36							
≤35	14	0	0	7	$P = 6.96 \times 10^{-3}$	4.16 (1.36–12.74)	$P = 3.79 \times 10^{-1}$	
≥35	22	17	0	5				
Multivariate analysis								
CINSARC NanoCind interpretable					$P = 1.91 \times 10^{-3}$	4.41 (1.64–16.43)		
GI					$P = 9.03 \times 10^{-2}$	1.84 (0.91–3.96)		
CINSARC NanoCind interpretable					$P = 3.14 \times 10^{-4}$	5.13 (1.95–18.90)		
Atypia					$P = 4.85 \times 10^{-2}$	1.96 (1–4.08)		

Note: Clinicopathologic data and correlation with CINSARC NanoCind signature and GI.
Abbreviations: A-NED, alive with no evidence of disease; AWD, alive with disease; CI, confidence interval; DOD, dead of disease.

RFS ($P = 3.07 \times 10^{-1}$; HR = 1.37 (0.76–2.48)]. At multivariate analysis, CINSARC and atypia for OS were both statistically significant although CINSARC had the strongest value [CINSARC: $P = 3.14 \times 10^{-4}$; HR = 5.13 (1.95-18.90); Atypia: $P = 4.85 \times 10^{-2}$; HR = 1.96 (1-4.08)].

Validation on an independent cohort

CINSARC NanoCind signature was applied to an independent series of 32 uterine leiomyosarcoma (23). Our signature was again predictive of metastasis [metastases-free survival (MFS) $P = 4.5 \times 10^{-2}$; HR = 3.2 (0.97–10.6)] and death [OS $P = 1.61 \times 10^{-2}$; HR = 8.46 (1.05–67.92); **Fig. 3A** and **B**].

Discussion

The strongest prognostic factor currently used in uterine leiomyosarcoma on the basis of therapeutic strategy is the stage (24). Most patients are diagnosed at stage I (localized, corresponding to a good prognosis). Nevertheless even at this stage, the metastatic relapse rate exceeds 50% (2). Until now, it has not been possible to distinguish, among patients with stage I uterine leiomyosarcoma, who will relapse and die of disease from those with long survival (9, 10).

Until now (2, 25–28), there is no clear evidence of the benefit of adjuvant chemotherapy in early stage uterine leiomyosarcoma. The FNLCC grading system failed to predict the outcome in uterine leiomyosarcoma (16). In 2014, the WHO was unable to recognize any grading system for uterine leiomyosarcoma as being universally acceptable for prognostic purposes, and the difficulty of proving the possible benefits of chemotherapy likely contributed to this overall uncertainty. These data weaken the value of the nomograms based on current histologic grading.

However, accurate prognostic factors in early stage uterine leiomyosarcoma are needed for guiding randomization in future chemotherapy and targeted therapy trials.

NanoCind signature: a powerful prognostic tool in uterine leiomyosarcoma

Our signature differentiates uterine leiomyosarcoma at any stage into a group with high risk of RFS and poor OS and another with better prognosis. Moreover, in clinical practice with stage I uterine leiomyosarcoma, which represents 60% of newly diagnosed tumors and for which there is no indication for adjuvant chemotherapy (8–10, 29–31), the CINSARC NanoCind signature identifies a group of patients (C2; ref. 32; 67.5% of this series) with a high risk of relapse and death, with 85.2% of death from disease and relapse. The strength of these data has been confirmed by the validation on an external series of uterine leiomyosarcoma from The Cancer Genome Atlas (TCGA) bioportal (ref. 27). These patients could be offered an adjuvant treatment and could be enrolled in the chemotherapy arm in ongoing and future clinical trials. On the other hand, those in the low-risk group (C1, 32.5% of the series) showing 61.5% of RFS could benefit from a prudential "wait-and-watch" strategy. This signature adequately identify the high-risk group (C2) but is less performant in the identification of low-risk group (C1) as five of 13 patients in the good prognostic group relapsed.

These findings are particularly interesting in an era in which the pertinence and utility of adjuvant chemotherapy for early stage tumors limited to the uterus are questioned (29, 30).

GI assessment by CGH array is a simple tool with a prognostic value, as we recently reported (17). Nevertheless, when one compares the prognostic power of the NanoCind signature with the GI, the former outperforms the latter in several aspects. First, NanoCind signature is prognostic not only for OS but also for RFS. Because relapse and the risk of metastasis are criteria used to decide upon adjuvant treatment, transcriptomic analysis is more informative than genomic profiling.

Second, the CINSARC signature is platform independent, as it has been tested with efficient and reproducible results on arrays (Affymetrix and Agilent), RNA-seq, and on NanoString Technology (19, 21, 32, 33). In addition, NanoString is far less influenced than RNA-seq by the poor quality of RNA extracted from FFPE blocks (21).

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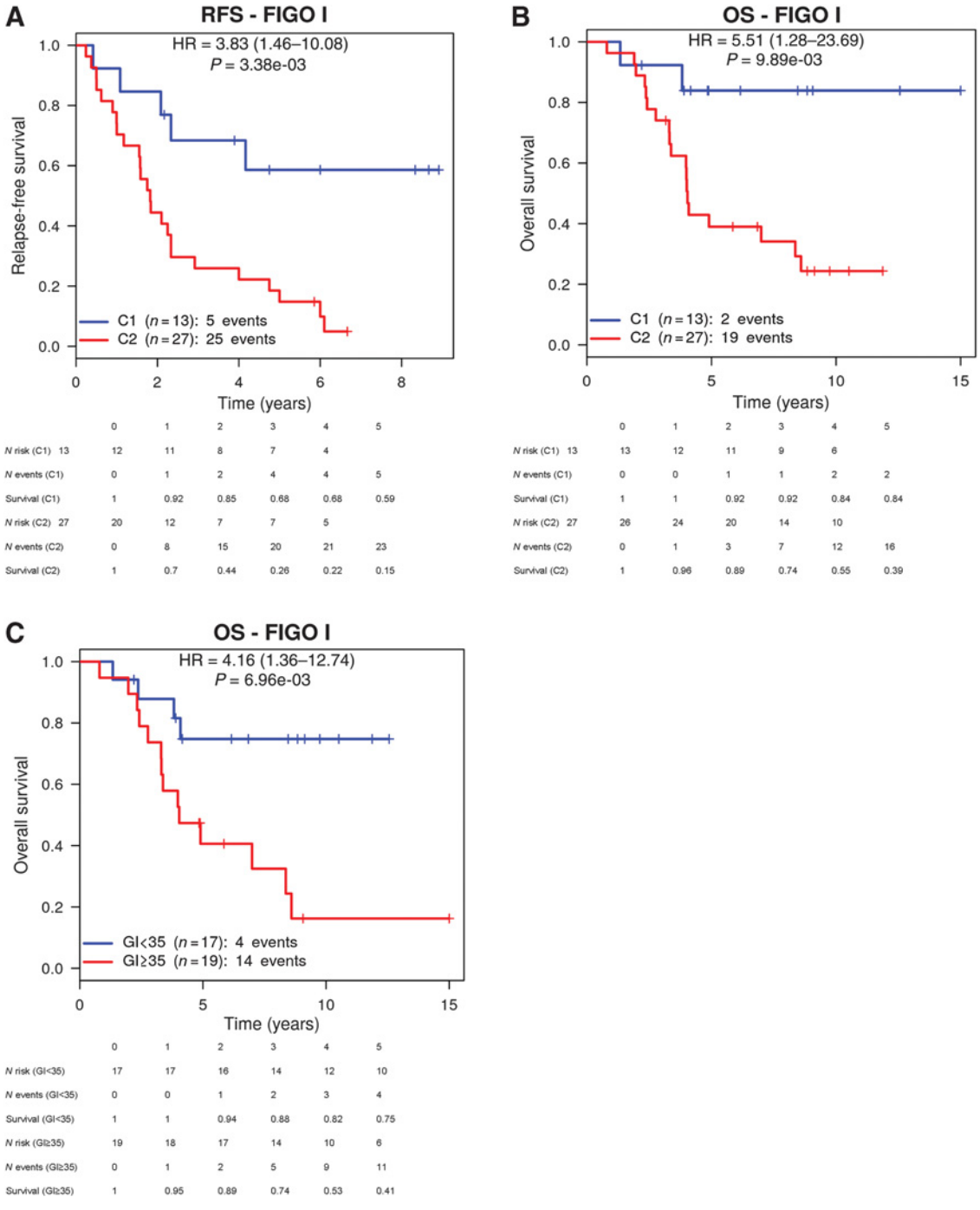

Figure 2.

RFS (**A**) and OS (**B**) for stage I uterine leiomyosarcoma according to CINSARC signature. **C,** OS for stage I uterine leiomyosarcoma according to GI at the cutoff of 35.

Unlike NanoCind, the GI is platform dependent, being strictly related to the resolution of the array. In our previous article, we established the cutoff of 35 on an Agilent platform of 8 × 60K (17). This value could change if the number of probes is higher (e.g., 4 × 180K) or the method for genomic hybridization is different (e.g., Agilent vs. Affymetrix Technology), and it needs to be validated on any new platform. Furthermore, NanoCind has the huge advantage of being ready to use. With the acquisition of NanoString technologies in many laboratories and molecular biology platforms, it will become more accessible.

Within the framework of a clinical trial led by the French Sarcoma group to evaluate prospectively the impact of NanoCind on patients' outcome, we have set up a network of NanoString users trained in CINSARC analysis and are developing a secure website where

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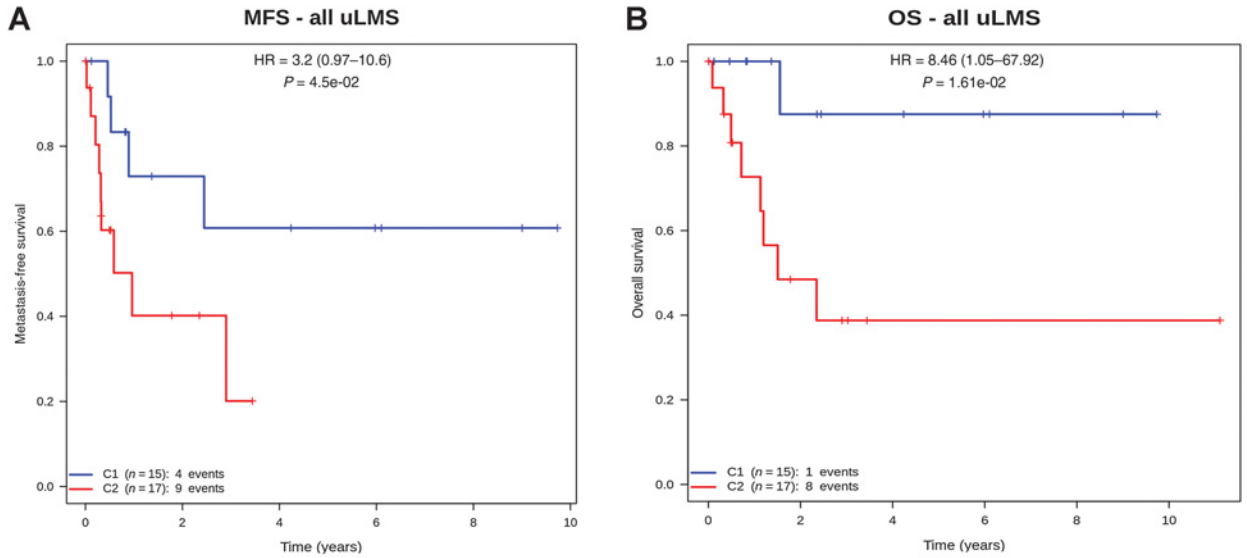

	0	1	2	3	4	5
N risk (C1)	15	7	6	5	5	4
N events (C1)	0	3	3	4	4	4
Survival (C1)	1	0.73	0.73	0.61	0.61	0.61
N risk (C2)	17	4	3	1	NA	NA
N events (C2)	0	8	8	9	NA	NA
Survival (C2)	1	0.4	0.4	0.2	NA	NA

	0	1	2	3	4	5
N risk (C1)	15	9	7	5	5	4
N events (C1)	0	0	1	1	1	1
Survival (C1)	1	1	0.88	0.88	0.88	0.88
N risk (C2)	17	9	5	3	1	1
N events (C2)	0	4	7	8	8	8
Survival (C2)	1	0.73	0.48	0.39	0.39	0.39

Figure 3.
MFS (**A**) and OS (**B**) for uterine leiomyosarcoma (uLMS) cohort from TCGA according to CINSARC signature.

clinicians will be invited to upload their NanoCind data and will receive the corresponding CINSARC classification. To accompany this evolution, these findings should now be confirmed in a larger independent cohort and even in a prospective setting.

The CINSARC NanoCind signature has now demonstrated its powerful prognostic value in a retrospective cohort of 60 uterine leiomyosarcoma (67% of whom presented at stage I) in RFS and OS at all stages including stage I by outperforming FIGO staging and GI assessment by CGH array. These data have been validated on an external cohort from TCGA data. It should therefore now be considered as the best prognostic tool for randomization in future clinical trials evaluating adjuvant treatment in stage I uterine leiomyosarcoma. The adjuvant arm could be offered to patients in the high-risk (C2) groups, while the observation arm could include low-risk (C1) patients.

Disclosure of Potential Conflicts of Interest

D. Querleu is a paid consultant for Arquer Diagnostic. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Croce, C. Valle, L. M'Hamdi, G. Pérot, E. Stoeckle, Q. Fontanges, M. Devouassoux-Shisheboran, F. Guyon, A. Floquet, G. MacGrogan, I. Soubeyran
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Writing, review, and/or revision of the manuscript: S. Croce, T. Lesluyes, E. Stoeckle, J.-C. Noël, D. Querleu, A. Floquet, C. Chakiba, G. MacGrogan, S.L. Guellec, F. Chibon
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Study supervision: F. Chibon

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