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Expanding the molecular spectrum of tenosynovial giant cell tumors

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Background: While great advances in clinical and pathological description of tenosynovial giant cell tumors (TGCT) have been made, TGCT molecular heterogeneity represents an ongoing challenge. The canonical oncogenic fusion *CSF1::COL6A3* is not systematically observed, suggesting that other oncogenic mechanisms are involved in tumorigenesis. This study aims to explore by RNA sequencing a retrospective series of tumors diagnosed as TGCT, in order to provide a better description of their molecular landscape and to correlate molecular features with clinical data.

Methods: We analyzed clinicopathological data and performed whole-exome RNA sequencing on 41 TGCT samples.

Results: RNAseq analysis showed significant higher *CSF1* and *CSF1-R* expression than a control panel of 2642 solid tumors. RNA sequencing revealed fusion transcripts in 14 patients including 6 not involving *CSF1* and some previously unreported fusions. Unsupervised clustering on the expression profiles issued from this series suggested two distinct subgroups: one composed of various molecular subtypes including *CSF1* and *FN1* rearranged samples and one composed of four tumors harboring an *HMG2::NCOR2* fusion, suggesting distinct tumor entities. Overall, 15 patients received at least one systemic anti-*CSF1R* treatment and clinical improvement was observed in 11 patients, including patients from both clusters.

Discussion: This study reported molecular heterogeneity in TGCT, contrasting with the clinical and pathological homogeneity and the ubiquitous high *CSF1* and *CSF1R* expression levels. Whether molecular diversity may impact the efficacy of systemic treatments needs to be further investigated.

KEYWORDS

tenosynovial giant cell tumor (TGCT), *CSF1*, *CSF1* fusion transcript, RNAseq analysis, expression profile, gene fusions

Introduction

Tenosynovial giant cell tumors (TGCT) also called pigmented villonodular synovitis (PVNS) are rare tumors of unknown etiology that develop in the synovial tissue in young adults. TGCT are classified as localized type or diffuse type according to the extent of synovial involvement and the location (1, 2). Localized forms (l-TGCT) are often benign, non-destructive, well-circumscribed nodular in shape and mainly located distally in the limbs (3). On the other hand, diffuse types (d-TGCT) more often involve larger joints, especially the knee and are considered locally aggressive by the 2020 WHO Classification of Tumors of Soft Tissue and Bone (4).

Initially considered as an inflammatory reactive process, cytogenetic studies revealed recurrent translocations of 2q37 and 1p13 chromosomal loci involving *COL6A3* (encoding collagen type VI $\alpha 3$) and *CSF1* genes in a subpopulation of tumors (5) and showed that TGCT is a neoplastic process with a locally destructive clinical behaviour. The resulting fusion protein is cleaved and leads to uncontrolled CSF1 (colony-stimulating factor 1) secretion by tumor cells, which attracts non-neoplastic cells (ie, macrophages and monocytes) expressing the CSF1 receptor (CSF1R), *via* a paracrine effect (5).

The treatment of these tumors is mainly surgical but several systemic treatments have been investigated in case of local recurrence and/or locally advanced diseases (d-TGCT) (6–8). Imatinib, which inhibits CSF1-R among other group III receptor tyrosine kinases, has shown a good efficacy with 93% of disease control (9). Other more potent and selective tyrosine kinase inhibitors (TKI) targeting CSF1-R and anti-CSF1R monoclonal antibodies (mAbs) have been investigated (10–12).

More recent reports suggest that not all TGCT harbor a *CSF1::COL6A3* gene fusion and other rearrangements have been reported such as *CSF1::VCAMI*, *CSF1::FNI* and *CSF1::CDH1* fusions (13, 14). We herein describe clinicopathological and molecular features in a retrospective series of TGCT patients from the Centre Leon Berard, using RNA-sequencing.

Methods

Tumors samples

This monocentric retrospective translational research program was performed between November 2016 and November 2021 on tumor samples from an investigational cohort of 41 TGCT patients from the Centre Léon Bérard (Lyon, France). The inclusion criteria for the investigational cohort were: 1) histopathological diagnosis of TGCT centrally reviewed 2) sufficient available tumor material. All samples consisted of Formalin-Fixed Paraffin-Embedded (FFPE) tissues samples provided by the pathology department and collected by biopsy or surgical excision at initial diagnosis. The study was

performed according to the French laws at the time of the initiation of the study and followed the principles of the Declaration of Helsinki. Oral consent was obtained after a detailed explanation to the patients or legal representatives for minors as reported in the patient's medical record. As the study was not interventional, formal written consent was not required by French law. The Centre Léon Bérard Clinical Trial Review Committee (Local Review Board) reviewed and agreed with the study protocol and this consent procedure.

Clinical review

Clinical follow-up was obtained from local medical records or provided by corresponding clinicians. Follow-up was reported from the date of diagnosis.

Histopathological, RNA sequencing and gene expression

The diagnosis was confirmed by histopathological analysis and all cases of the series were reviewed by expert pathologists from the NETSARC+ network. Integrative whole-exome RNA sequencing and transcriptomic analysis was performed as previously described, with FFPE material from tumor biopsy or resection and before any systemic treatment (15).

Statistical analysis

Patients and tumor characteristics were described using mean and range for continuous variables and percentages for categorical variables. Statistical analyzes and figures were performed with R software.

Results

Patients, clinical and pathological findings

This study identified 41 patients diagnosed with TGCT tumors (Figure 1). The clinical characteristics of the patients are presented in Table 1. The sex ratio was 1.4 and the mean age at diagnosis was 36.9 years (range 9-74 years), with a majority of d-TGCT (57%) as compared to l-TGCT. The knee joint was affected in 48% of cases and the ankle in 17% of cases. Other anatomical locations such as the feet, hands, hips and shoulders could also be affected. The main symptoms were pain (57%), swelling (53%) and limited range of motion (25%). Imaging identified lesions with different periarticular sizes and joint involvement (thickening of the synovium) in 71% of the cases,

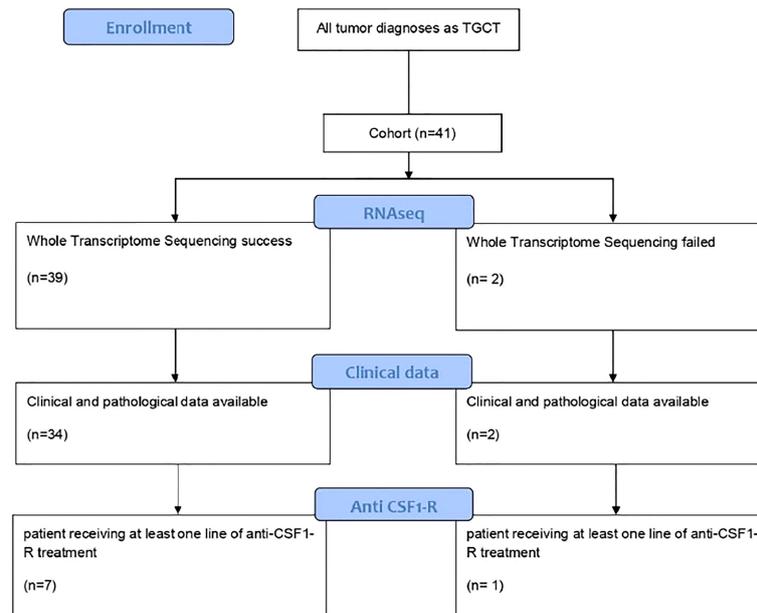


FIGURE 1
Cinsort diagram of patients included in the study.

hemosiderin deposits visible in T2 gradient echo on MRI in 18% of the cases and lytic bone lesions in 18% of cases. Histology revealed histiocyte-like or epitheloid-like mononuclear cells in 100% of the cases, giant osteoclast-like plurinuclear cells in 91% of the cases, hemosiderin deposits with siderophages in 79% of the cases and foamy histiocytes in 58% of the cases. The lesion was more or less infiltrative or encapsulated depending on its localized or diffuse nature.

RNA sequencing analysis

All but two RNA-sequencing (RNA-seq) had successful quality controls (reads > 10M). Supervised analyses highlighted upregulation of *CSF1* and *CSF1-R* in all tumors (Figure 2) and this overexpression was significantly higher compared to a control panel of 2642 solid tumors with more than 240 different molecular subtypes (15). A chromosomal rearrangement was identified in 36% of the cases ($N=14$), with 8 of them involving *CSF1*. The fusion genes detected are shown in Figure 3. Considering the 8 cases with translocations involving *CSF1*, the fusion partners were respectively *FN1* ($N=2$), *CD101* ($N=2$), *COL6A3*, *PRG4*, *TNC* and *CDH17*. The other fusion transcripts detected were *HMGA2::NCOR2* ($N=4$), *FN1::PRG4* and *FN1::NUBPL1*.

Unsupervised consensus hierarchical clustering divided the samples into two main groups/cluster. Cluster C1 ($N=4$) contained all the four *HMGA2::NCOR2* samples while cluster C2

($N=35$) grouped various molecular subtypes, including *CSF1*-fused and *FN1*-fused samples. With a 3-dimensional principal component analysis, the 3-dimension explaining 7.5% of the total variation was due only to tumors with an *HMGA2::NCOR2* fusion (Supplementary Figure 1). Significant difference between groups was observed with RNA-seq (Supplementary Figure 2). This difference is not likely to be related to microenvironment. (Supplementary Figure 3). The microenvironment was explored and the immune infiltrate was composed of dendritic cells, monocytes and non-M1 macrophages. This difference is also evidenced with RNA-seq results using Volcano plots showing different gene expression in C1 and C2 (Supplementary Figure 4). Mutations detected consisted all of variants of uncertain significance (*ATM*, *POLE*, *KMT2D*, *SMARCA4*, *TET2*, *GNAQ*, *BRCA2*, *PDGFRA/B* and *KIT*) except one case with a single nucleotide variant on the exon 13 of *CSF3R* (C.G1640A: P.W547x).

Surgical and medical management

Among the 41 patients, 36 patients had detailed clinical management available. Among them, 11 patients ($N=11/36$, 31%) experienced initial surgery including five ($N=5/11$, 45%) who had a recurrence after surgery. Mean time to relapse was 15.2 [3-48] months.

Fifteen patients received at least one systemic treatment targeting the *CSF1/CSF1-R* axis, eight received at least 2 lines of treatment and two patients received 3 lines of systemic

TABLE 1 Clinical characteristics of the investigational series of TGCT.

| | |
|--------------------------------|-------------------|
| N | 41 |
| Mean Age (years); range | 36.9; 9-74 |
| Sex ratio (M/F) | 1.4 |
| Location | |
| Knee | 17 |
| Ankle | 6 |
| Hand | 3 |
| Foot | 3 |
| Other | 6 |
| N/A | 6 |
| Type | |
| Localized | 12 |
| Diffuse | 16 |
| N/A | 13 |
| Main symptoms | |
| Pain | 16 |
| Swelling | 15 |
| Limited range of motion | 17 |
| N/A | 13 |
| Radiological lesions | |
| Joint involvement | 20 |
| Hemosiderin deposits | 5 |
| Bone lysis | 5 |
| N/A | 13 |
| Anatomopathology | |
| Mononuclear cells | 34 |
| Giant plurinuclear cells | 31 |
| Hemosiderin deposits | 27 |
| Foam cells | 20 |
| N/A | 7 |

N/A, not available.

treatment. The systemic therapies used were imatinib ($N=11$), pexidartinib ($N=4$), cabiralizumab ($N=4$), nilotinib ($N=2$) and emactuzumab ($N=1$). In the 15 patients treated with first line systemic treatment, two achieved a total improvement, 9 a partial improvement, three no improvement and 1 worsening of symptoms. Radiology revealed two complete response, 7 partial responses and 7 stable diseases. The mean duration of treatment was 10.8 months [1-54] and the mean relapse-free duration with this first line of systemic treatment was 25.9 months [2-64]. Treatments outcomes are detailed in Figure 4. Interestingly, a patient with an *HMGA2::NCOR2* gene fusion with an unresectable d-TGCT and achieved a CR with an anti-CSF1 TKI while a patient with a *FN1::NUBPI* fusion achieved a partial response after anti-CSF1 mAb therapy.

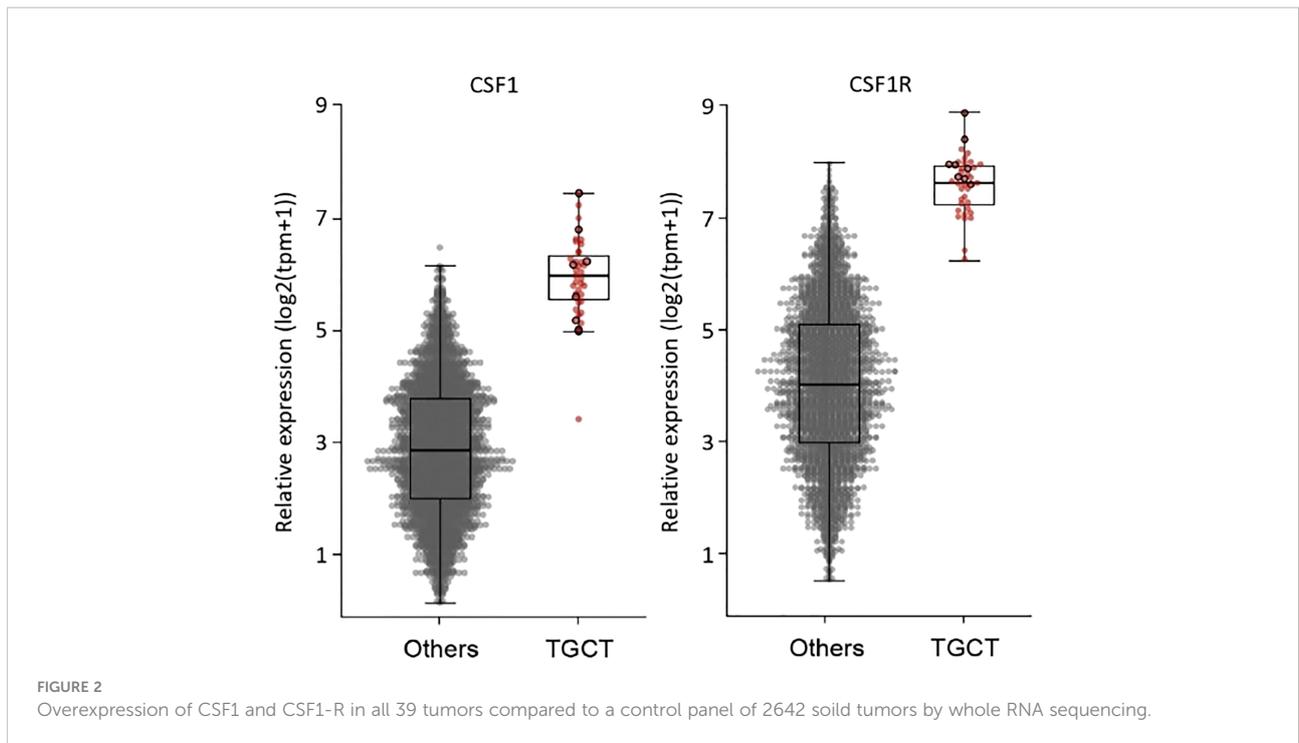
Discussion

The present work analyzed a retrospective series of 41 TGCT including 39 with a contributive RNA-seq. All the tumors

overexpressed *CSF1* and *CSF1-R*. The aberrant *CSF1* expression in the neoplastic cells attracts non neoplastic cells, then forming a tumor mass through a landscape effect as previously proposed by West et al. in 2006 (5). Surprisingly, the historical translocation involving *CSF1* and *COL6A3* was detected in only one patient, despite a prevalence is estimated at 33% in the literature (16). A previous cohort of 39 TGCT reported no cases harboring the *COL6A3::CSF1* fusion using FISH and RNA-seq technics (14). Our results expand the molecular spectrum of this rare conjunctive tumor and a variety of genomic alterations is identified in this series. Interestingly, RNA-seq enabled us to suggest two groups combining gene fusion identification and expression profiling. The C2 group gathered TGCT harboring a fusion of *CSF1* and/or *FN1* while the C1 group is composed of tumors harboring an *HMGA2::NCOR2* fusion.

Overall, four samples harbored the *HMGA2::NCOR2* gene fusion, identified as the most represented fusion in our cohort. These fusions all showed a breakpoint was on *HMGA2* exon 3 and on *NCOR2* exon 14 or 15. The *HMGA2::NCOR2* fusion brings together a DNA-binding motif encoded by *HMGA2* exons 1-3 with *NCOR2* exons 16-47 encoding two repressor domains, a binding site for histone deacetylase 3 (HDAC3) and binding sites for several nuclear hormone receptors and transcription factors. Whether this fusion regulates the expression of *CSF1* is still unknown and the underlying molecular mechanisms remain elusive. Fusion genes involving *HMGA2* have also been detected in various tumor types such as lipomas leiomyomas, pleomorphic adenomas of the salivary gland, cervical polyps and hemangiopericytomas (17). This *HMGA2::NCOR2* fusion has recently been described in a series of 6 "giant cell tumors of soft tissue" (18) and in a series of 6 "osteoclastic giant cell-rich tumors of bone" (19). Unfortunately, expression of *CSF1* was not detailed in these publications. In the four tumors harboring *HMGA2::NCOR2* fusion, two were identified in patients with a very atypical clinical presentation (soft tissue and temporal bone lesions). The distinctive clinical and genomic features strongly suggest that they belong to a distinct entity.

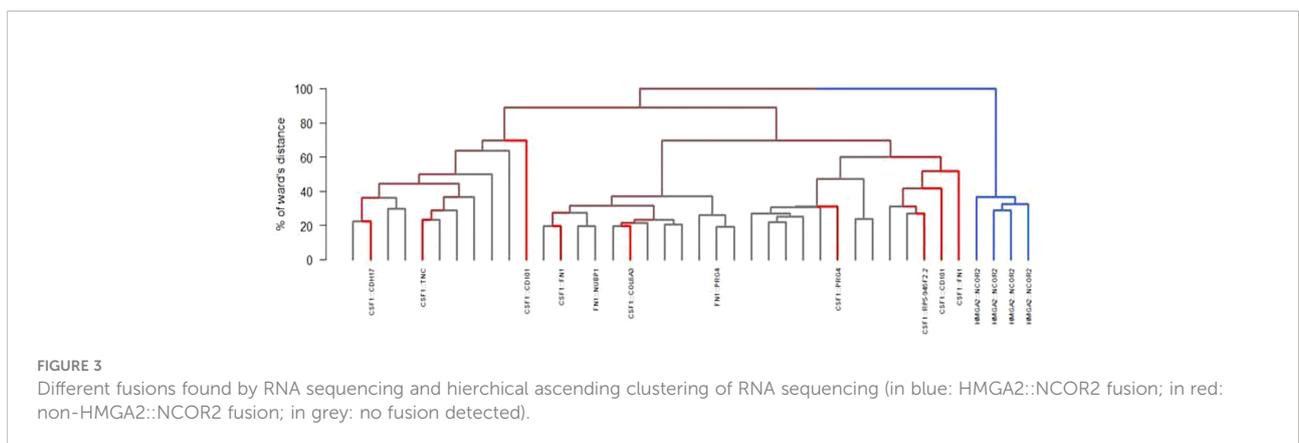
Regarding the translocations involving *CSF1*, the breakpoint was located on exon 5 in all but one case (one translocation on exon 6). These breakpoints may be responsible of *CSF1* overexpression in these tumors. Indeed, it is located downstream of exon 5, replaces or removes a long 3'UTR portion containing (AU)-rich elements known negative regulatory sequences of miRNA (14). We also identified some similarities with "non-COL6A3" *CSF1* partners, usually expressed and secreted by synovial cells at high expression level and structurally linked to the extracellular matrix proteins (FN1, PRG4, TNC, CDH17) and therefore modulating the microenvironment through autocrine and/or paracrine activation. Indeed, the fibronectin binds to the surface of cells and to various compounds, including collagen, fibrin,

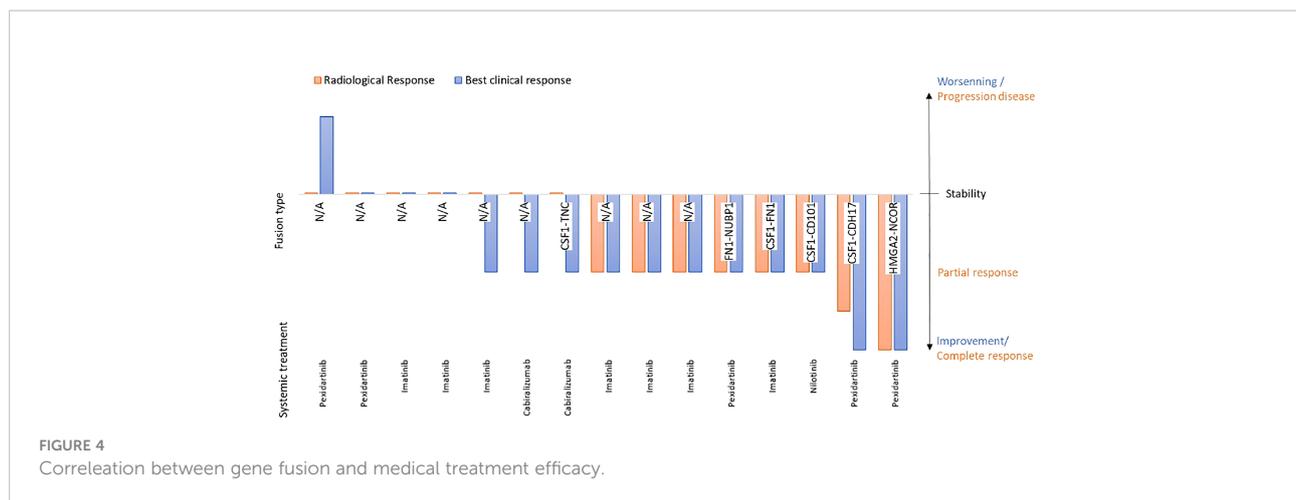


heparin and actin. Fibronectins are involved in cell adhesion, cell motility, opsonization, wound healing and maintenance of cell shape. They are involved in osteoblast compaction through the fibronectin fibrillogenesis cell-mediated matrix assembly process, essential for osteoblast mineralization, and in the regulation of type I collagen deposition by osteoblasts. The *FN1::FGFR1* fusion gene is detected in phosphaturic mesenchymal tumors with paraneoplastic osteomalacia (20) and *FN1* has also been recently described as a novel fusion partner of *ALK* in an inflammatory myofibroblastic tumor (21). In addition, *FN1* is significantly overexpressed in TGCT such as the glycoprotein PRG4 which is secreted by synovial fibroblasts

and superficial chondrocytes in the extracellular matrix and which regulates the proliferation of synoviocytes (22). *PRG4* has been identified as a fusion partner with *CSF1* but also with *FN1*, suggesting similar mechanisms.

While adequate surgical resection remains the treatment of choice for TGCT, d-TGCT is more difficult to resect and shows a higher rate of recurrence (up to 50%) (7, 23). Because TGCT is known to be associated with a *CSF1::COL6A3* fusion resulting in the overexpression of CSF1, systemic therapies targeting the CSF1/CSF1R axis (imatinib, nilotinib, emactuzumab, etc...) in patients with locally advanced and/or relapsed d-TGCT have been investigated and resulted in a very interesting clinical





activity with acceptable toxicity (9–12). Nevertheless, the efficacy of these treatments is difficult to assess using conventional imaging criteria (RECIST) since multinodular disease with bone damage and joint pain limit the interpretation. The clinical response is therefore crucial and it underlines the need for relevant scales for functional, pain, or quality of life assessments (24, 25). The optimal treatment duration and the adequate schedule for neoadjuvant or adjuvant treatment also requires further investigation. Our cohort confirms the good overall response to the CSF1-R inhibitor, including in tumors harboring more uncommon fusions such as *HMG2::NCOR2* (26) or *FN1::NUBP1*. Among the 11 patients who experienced initial surgery, five patients relapsed, which a mean time to relapse of 15.2 months. Of note, the mean relapse-free duration with a first line of systemic treatment was 25.9 months in our series.

To our knowledge, this study represents the largest series of RNA-sequenced TGCT. Altogether, TGCT represent a heterogeneous group of tumors in terms of genetics (27) including newly identified and some recurrent molecular variants. RNA-seq led to the reclassification of four “*HMG2::NCOR2* giant cell tumors”. The transcriptional similarities between the CSF1 transcripts and newly identified transcripts suggest an analogous oncogenic activation pathway (28), illustrated by the efficacy of CSF1 inhibitors in both situations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was not provided because As the study was not interventional, formal written consent was not required by French law. Ethical review and approval was not required for the animal study because as the study was not interventional, formal written consent was not required by French law.

Author contributions

TG carried out the data collection and the drafting of the article. MB coordinated the scientific project. FT was responsible for the bioinformatics analyses. HV actively participated in the different stages of data analysis and writing of the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.1012527/full#supplementary-material>

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