Targeting molecular alterations has been proven to be an inflecting point in tumor treatment. Especially in recent years, inhibitors that target the tyrosine receptor kinase show excellent response rates and durable effects in all kind of tumors that harbor fusions of one of the three neurotrophic tyrosine receptor kinase genes (NTRK1, NTRK2 and NTRK3). Today, the therapeutic options in most metastatic sarcomas are rather limited. Therefore, identifying which sarcoma types are more likely to harbor these targetable NTRK fusions is of paramount importance. At the moment, identification of these fusions is solely based on immunohistochemistry and confirmed by molecular techniques. However, a first attempt has been made to describe the histomorphology of NTRK-fusion positive sarcomas, in order to pinpoint which of these tumors are the best candidates for testing. In this study, we investigate the immunohistochemical expression of pan-TRK in 70 soft tissue and bone sarcomas. The pan-TRK positive cases were further investigated with molecular techniques for the presence of a NTRK fusion. Seven out of the 70 cases showed positivity for pan-TRK, whereas two of these seven cases presented an NTRK3 fusion. Further analysis of the fused sarcomas revealed some unique histological, molecular and clinical findings. The goal of this study is to expand the histomorphological spectrum of the NTRK-fused sarcomas, to identify their fusion partners and to correlate these parameters with the clinical outcome of the disease. In addition, we evaluated the immunohistochemical expression pattern of the pan-TRK and its correlation with the involved NTRK gene.

Keywords: sarcoma, prognosis, NTRK fusion, TRK immunohistochemistry, NTRK fusion partner, histology

INTRODUCTION

Soft tissue and bone tumors are a very heterogenous group of neoplasms which makes prognosis difficult to assess. Moreover, given their rarity of occurrence, standardization of diagnostic criteria and precise treatment protocols is challenging. The majority of localized sarcomas are treated with excision mostly followed by adjuvant radiotherapy to control local recurrence [1, 2]. Few sarcoma types are chemo-sensitive, such as rhabdomyosarcoma, osteosarcoma and Ewing sarcoma [2, 3]. In the metastatic setting, the 5-year overall survival rates do not exceed 20%, highlighting that effective
The treatment of advanced disease remains a challenge. There is clear need for new therapeutic options in advanced sarcomas [4].

Some of the molecular alterations that are found in tumors are druggable and this has been a significant turning point in cancer treatment. One of the most important representatives are tyrosine kinase inhibitors (TKI) that are used for the treatment of diverse tumor types, such as imatinib for gastrointestinal stromal tumors (GIST) [5]. Unfortunately, today most of the oncogenic driver alterations remain undruggable.

Very recently, it has been proven that tumors with fusions of one of the three neurotrophic tyrosine receptor kinase genes (NTRK1, NTRK2 and NTRK3) can be treated with tyrosine receptor kinase (TRK) -inhibitors. The first generation TRK-inhibitors, larotrectinib and entrectinib [6], show excellent response rates and durable effects in tumors that harbor fusion of one of the NTRK genes, regardless of tumor type or site of origin. The adverse events are well tolerated. Still, a major obstacle for those inhibitors is the development of resistance. Therefore, new generation TRK-inhibitors are developed, such as LOXO-195 and repotrectinib [7, 8].

Despite the promising results of TRK-inhibition, NTRK fusions are rare genetic events. Among sarcomas, infantile fibrosarcomas show fusions of the NTRK3 gene in more than 90% of the cases [9]. The rates of NTRK fusions in the remaining sarcoma types are unfortunately very low. Moreover, no clear morphologic criteria are established for the recognition of the NTRK-fused sarcomas. A NTRK fusion has to be demonstrated by means of molecular analysis. Immunohistochemistry can be performed as an enrichment strategy to select tumors for subsequent molecular analysis. In a previous publication, we suggested an algorithm for determining which sarcomas are more likely to carry this fusion [10].

In this study, we investigated the expression of the pan-TRK antibody in different types of soft tissue and bone tumors by immunohistochemistry and we correlated the expression of the positive cases with the presence of NTRK fusions. Furthermore, we summarized the clinicopathological characteristics, in an attempt to give more information about the identification of these tumors, in conjunction with the cases that are described in the literature.

**MATERIALS AND METHODS**

**Tissue Samples**

Archival formalin-fixed paraffin embedded (FFPE) tissue samples from 70 patients with soft tissue and bone tumors were retrieved from the Department of Pathology at the Antwerp University Hospital. The tissue samples were collected from biopsy material as well as excision specimens. The material was not older than 5 years, to avoid loss of immunoreactivity and to obtain quality material for the additional molecular analysis. The biopsies were fixed in 4% formaldehyde for up to 12 h while the excision samples were fixed for up to 32 h.

Inclusion criteria were all locally aggressive and malignant soft tissue tumors, except infantile fibrosarcoma, given their known molecular status with NTRK3 fusions [9]. This was the only exclusion criterion, while all age groups and ethnicities were incorporated.

All methods were carried out in accordance with relevant guidelines and regulations.

| TABLE 1 | Tumor characteristics. |
|---------|-------------------------|
| **Characteristics** | **Number (n)** |
| Gender | |
| Male | 46 |
| Female | 24 |
| Tumor location | |
| Bone | 19 |
| Deep soft tissue extremities | 17 |
| Deep soft tissue trunk and back | 5 |
| Deep soft tissue head and neck | 4 |
| Skin and subcutaneous fat tissue | 12 |
| Abdomen | 6 |
| Mediastinum | 5 |
| Retroperitoneum | 2 |
| Histological type | |
| Chondrosarcoma | 10 |
| Ewing sarcoma | 3 |
| Osteosarcoma | 5 |
| Angiosarcoma | 7 |
| Kaposi sarcoma | 8 |
| Leiomyosarcoma | 5 |
| Liposarcoma | 9 |
| Myxofibrosarcoma | 5 |
| Rhabdomyosarcoma | 3 |
| Synovial sarcoma | 3 |
| Sarcoma NOS | 12 |
| Grade | |
| High grade | 48 |
| Low grade | 18 |
| Not known | 4 |
| Local or metastatic disease | |
| Local aggressive | 15 |
| Monometastatic disease | 11 |
| Multimetastatic disease | 13 |
| No local recurrence or metastatic disease reported | 31 |
| Oncogenic mechanism | |
| Oncogenic mechanism known | 14 |
| Not known oncogenic mechanism | 48 |
| Oncogenic virus (HIV) | 8 |
| Survival | |
| Alive | 42 |
| Death from disease | 22 |
| Death from other cause | 6 |
| Medical history | |
| No medical history | 56 |
| HIV | 5 |
| Lymphoma and HIV | 1 |
| Lymphoma and other tumors | 1 |
| Epithelial tumor | 5 |
| Melanoma | 1 |
| Syndrome | 1 |
| Therapy | |
| Excision only | 28 |
| Excision + adjuvant therapy | 28 |
| Neoadjuvant CHMT | 12 |
| Not known | 2 |
| **Abbreviations:** n, number; NOS, not otherwise specified. |
| *Adjuvant therapy was either chemotherapy or radiotherapy or immunotherapy or targeted therapy or protontherapy or their combinations.*
As it was a retrospective study on archival material, no informed consent of the patients could be obtained. We received approval by the Ethics Committee of the Antwerp University Hospital/University of Antwerp (EC 18/45/517) to use historical samples without additional informed consent from the patients.

**Immunohistochemistry**

As a reference method we used the VENTANA pan-TRK assay (clone EPR17341) performed according to the instructions of the vendor on a Benchmark Ultra (Ventana Medical Systems, Tucson, AZ, United States). This widely used EPR17341 clone is reactive with a conserved proprietary peptide sequence from the C-terminus of TRKA, TRKB and TRKC, and is therefore reactive with any of the oncogenic TRK proteins, although a lesser sensitivity for \( \text{NTRK3} \) fusions is described.

We looked at the expression of TRK in the tumor cells. All stained slides were assessed and scored independently by two pathologist (VS. and PP). Tumors were considered positive if \( \geq 1\% \) of tumor cells exhibit staining at any intensity above background \([11, 12]\). In addition, the different subcellular staining patterns (cytoplasmic, membranous, nuclear and perinuclear) were all considered to be positive. Moreover, for the evaluation of the immunohistochemical staining we also used the modified Histoscore (H-score) \([13]\). This is a semiquantitative assessment of both intensity and staining and the percentage of positive cells.

Evaluation of the slides was based on scanned slides at a Philips platform.

**Molecular Techniques**

The \( \text{NTRK} \) fusion status and possible fusion partner of the samples was confirmed by next generation sequencing (NGS). Targeted RNA-based NGS was conducted with the Oncomine Focus Assay (OFA) panel (Thermo Fisher Scientific, San Francisco, CA, United States) on an S5 instrument, according to the manufacturer’s recommendations.

**RESULTS**

### Pan-TRK Immunohistochemical Expression in Diverse Tumor Types and Correlation With \( \text{NTRK} \) Fusions

We investigated the immunohistochemical expression of TRK in diverse types of soft tissue and bone tumors. Tumor characteristics are summarized in Table 1.

Among the different tumor types, seven tumors (10%) displayed immunohistochemical positivity for pan-TRK in the tumor cells. The remaining 63 tumors showed no pan-TRK expression. The immunohistochemical expression of these seven cases according to the H-score is illustrated in Table 2.

Among the positive tumors there were two alveolar rhabdomyosarcomas, one epithelioid angiosarcoma, one malignant peripheral nerve sheath tumor (MPNST), one osteosarcoma and two spindle cell sarcomas, not otherwise specified (NOS). All but one were reported as high grade tumors. The low-grade tumor was a spindle cell sarcoma NOS.

NGS RNA analysis was performed in all positive cases. Two out of these (nearly 28,6% among the pan-TRK positive cases and 2,86% among all tumors included in this study) showed an \( \text{NTRK} \) fusion, while the rest did not. The characteristics of the tumors with the fusion are summarized in Table 3.

### A Low-Grade Spindle Cell Tumor With an \( \text{ETV6-NTRK3} \) Fusion

The first case concerned a 10 year-old male with a cutaneous tumor on his finger. The duration of the lesion could not be
determined accurately but was estimated by the parents to be six to seven years. No previous operations or other therapies were mentioned.

Macroscopically, there was a polypoid lesion that measured approximately 5 mm (Figure 1A). Microscopy revealed a dermal spindle cell proliferation. The cells were arranged in a fascicular pattern. There was some variation in size and shape but there was no striking pleiomorphism. Mitotic activity was present (up to 5 mitosis/10 high power fields), but no necrosis was perceived. There was local mucin deposition between tumor cells. Finally, some blood vessels within the tumor showed hyalinization and presence of multinucleated cells (green arrow) (Figure 1B). A wide range of immunohistochemical stainings were performed, such as CD68, SMA, desmin, EMA, mucin 4, SOX10, S100 and CD34, from which we could not deduce a specific differentiation line of the tumor cells. More specifically, CD68 and SMA stained focally, while the rest was negative. Moreover, immunohistochemical examination for Anaplastic Lymphoma Kinase (ALK) proved to be negative.

The tumor was located in the dermis with focal extension into the subcutis. The lesion was completely removed but with narrow margins.

Nuclear positivity of the tumor cells for pan-TRK was noticed on immunohistochemistry (Figure 1C). The NGS analysis revealed an ETV6-NTRK3 fusion (1,328 reads out of a total of 52,464 mapped fusion panel reads). The patient underwent positron emission tomography–computed tomography (PET-CT) but no metastatic lesions could be detected. No signs of local recurrence or disseminations were noticed almost a year after the excision.

A High-Grade Spindle Cell Tumor With a TFG-NTRK3 Fusion

The second case concerned a 19 years-old man. The patient presented with a tumor on the antero-external side of the right tibia dating for several months. The tumor was located intramuscularly with extension to the subcutaneous fat tissue. Three months after the first examination, the tumor was excised. Macroscopically, an almost 14 cm large mass was seen. Microscopy revealed a multinodular lesion that was partially surrounded by a thin capsule. Spindle-shaped tumor cells with a fascicular growth pattern were noticed. Thickened collagen bundles were seen in between tumor cells, as well as areas with calcification and ossification (Figure 2A). There was high mitotic activity and also necrosis. After extensive immunohistochemical analysis, including antibodies against pan-cytokeratin, S100, CD34, beta-catenin, SMA, desmin, CD10 and MDM2, the tumor was classified as high-grade spindle cell sarcoma NOS. Again here, immunohistochemistry for S100 and CD34 was negative. Despite the fact that the tumor was completely excised, given its high-grade, the patient received adjuvant radiotherapy. Four months after the excision the patient developed multiple lung metastases, which were treated with radiotherapy. Immunohistochemistry on the material from the first excision revealed a cytoplasmatic positivity for pan-TRK in the majority of the tumor cells (Figure 2B). NGS analysis showed the presence of a TFG-NTRK3 fusion (424 reads out of a total of 2,668 mapped fusion panel reads). The patient started with larotrectinib at a dose of 100 mg twice daily. The patient was still alive a month after the initiation of treatment and was then lost from follow-up.

DISCUSSION

TRK is a member of the tyrosine kinase family, predominantly known for its role in neuronal cell differentiation. There are three receptors (TRK A, B, and C) encoded by the three NTRK genes, NTRK 1, 2, and 3, respectively [9]. TRK is a transmembrane receptor, that upon its binding with a ligand, undergoes
drugs have a high response rate and durable responses [14, 15]. Tumors where not of a histologic type that carries a specific tumor [16]. Thus, sarcomas with a known driver oncogenic fusion show no other actionable alterations within the fusions of one of the other specific [17].

Hence, detection of sarcoma, are less likely to harbor fusions of one of the three alteration, as for instance alveolar rhabdomyosarcoma or synovial sarcoma might not have any diagnostic or therapeutic value [17].

While testing in sarcomas with a canonical oncogenic alteration be prioritized in sarcomas with high genetic alteration. Consequently, testing for NTRK fusions should be prioritized in sarcomas with high NTRK fusion frequency, while testing in sarcomas with a canonical oncogenic alteration might not have any diagnostic or therapeutic value [17].

Currently, correct identification of NTRK-fused sarcomas is only possible by means of molecular techniques. However, recently there have been attempts to describe the morphological features of tumors carrying this molecular alteration. To date, various morphological features have been described in NTRK-fused sarcomas, the most consistent being spindle cell morphology [10]. Growth patterns attributed to these tumors are summarized in our previous review[10] and include lipoblastomatosis-like [18, 19], hemangiopericytoma-like [20], fibrosarcoma-like [21–23], neoplasms resembling inflammatory myofibroblastic tumors [24, 25] and dermatofibrosarcoma protuberans-like [26]. Moreover, spindle cell tumors with myxoid features [27] as well as characteristic blood vessels with perivascular thick collagen deposition [28] are also reported.

On a molecular basis, NTRK fusions are the driving oncogenic mechanisms, with fusions of the NTRK3 gene being the most frequent, followed by fusions of the NTRK1 gene, while only a few show NTRK2 fusions [10].

In our case, both tumors with NTRK fusion presented with a spindle cell morphology. None of the tumors showed a characteristic growth pattern like those previously mentioned. It is suggested that the majority of the NTRK-rearranged mesenchymal neoplasms display a combination of morphological patterns, which could be a helpful clue in tumor recognition [29]. Indeed, one of the tumors that we present also showed hyalinization of the blood vessels while the other displayed thickened collagen bundles within the tumor cells.

In many cases in literature, the tumors expressed CD34 and/or S100-protein on immunohistochemistry [18–23, 26, 28, 30]. None of the NTRK-fused cases in our series were positive for these immunohistochemical markers. However, this could be a useful diagnostic tool in cases of a spindle cell tumor without a specific growth pattern, in order to pinpoint those neoplasms that need further investigation for the presence of the fusion.

Pan-TRK immunohistochemistry is a reliable screening method for the detection of NTRK fusions with sensitivity and specificity exceeding 95% [12, 31]. Careful interpretation of the immunohistochemical staining is though recommended, since its specificity is low in sarcomas with neural or myogenic differentiation, as wild-type TRK protein is physiologically expressed in neural and smooth muscle tissue [32].

In our samples, two out of the seven immunohistochemical positive cases (nearly 28.6%) correlated with the presence of a NTRK fusion. This is in line with a very recently published study of Nozzoli et.al., where two of the eight immunohistochemical positive cases that had available RNA material for NGS, proven to harbor an NTRK fusion [33]. The ratio of sarcomas with a fusion in relation to the total population of the 70 cases examined in our series is approximately 2.8%. False-negative cases, with negative pan-TRK immunohistochemistry while the tumor was proven to harbor a NTRK fusion, are rarely described [29, 31, 34]. The staining pattern of the antibody also varies in intensity and localization. Different subcellular staining patterns have been documented such as cytoplasmic, cell membranous, nuclear with or without peri-nuclear accentuation, all of which are considered as positive [22, 31, 35, 36]. All these staining patterns suggest the presence of the fusion, and molecular testing is needed for confirmation. Subsequently, there has

![FIGURE 2](image-url)
been an attempt to demonstrate a correlation between the staining pattern and the NTRK gene fusion. Hence, it has been shown that fusions of the NTRK1 gene mostly correlate with a diffuse cytoplasmic staining, while nuclear and rather weak pan-TRK staining is frequently mentioned with NTRK3 gene fusions [29]. Furthermore, nuclear positivity is correlated with ETV6-NTRK3 fusion in different tumor types [31, 37]. This is consistent with our findings, where one of the tumors showed pan-TRK weak nuclear positivity, and this tumor harbored an ETV6-NTRK3 rearrangement.

The prognosis of NTRK1- and NTRK3- fused sarcomas in correlation with histomorphology, has also been a subject of investigation. Sarcomas with NTRK1 gene fusions can present a low- or a high-grade histomorphology. While morphologically high-grade NTRK1-fused tumors display an aggressive course in the majority of the cases, morphologically low-grade NTRK1-fused sarcomas can have a favorable clinical course [10, 38]. On the other hand, sarcomas with fusions of the NTRK3 gene and especially those with ETV6 fusion partner, are mainly aggressive neoplasms, even those with intermediate cytological atypia [10, 39]. Low-grade cytomorphology is usually not a feature of these fusions. This is in contrast with our findings. We describe a tumor with ETV6-NTRK3 fusion with a rather indolent course. The tumor was present for almost six to seven years prior to the diagnosis and showed no signs of recurrence or metastatic spread almost a year after the excision. Morphologically, the tumor showed a cellular spindle cell proliferation without pronounced cytological atypia; mitotic activity was apparent but rather limited, while no necrosis was seen. An interesting feature was the hyalinization and presence of multinucleated cells in the blood vessel wall.

In addition, we describe a TFG-NTRK3 fused sarcoma with an aggressive course. From a histological point of view, the tumor was a high-grade neoplasm with marked cytological atypia, increased mitotic activity as well as areas of necrosis. No CD34 or S100-protein expression was observed. The patient also developed disseminated disease. These findings are again in contrast with the features of the limited TFG-NTRK3 fused mesenchymal tumors documented in the literature [18, 39]. TFG-NTRK3 sarcomas are amongst the rare NTRK3-fused sarcoma cases with a rather favorable histological and clinical picture. Opposite to our case, the tumors are known to display mostly an intermediate cytological grade or a lipofibromatosis-like morphology. Immunohistochemical positivity of the neoplastic cells with CD34 and S100-protein were documented, in contrast to our case. The prognosis of these tumors is reported favorable with no evidence of recurrence or metastasis in the (rather limited) follow up period.

Among these two tumors, the one with the best prognosis was a superficial lesion on the acral skin, while the one with the worst clinical course was located in the deep soft tissues. It therefore seems that in addition to the presence of an NTRK fusion, tumor location might also has a prognostic value.

![Figure 3](https://example.com/figure3.png)

**FIGURE 3** | Schematic illustration of the TRK signaling pathway and its role to cell differentiation. Created with BioRender.com.
Conclusion

NTRK fusions are rare genetic events that can appear in a wide range of tumor types, including mesenchymal tumors. Identification of rearrangement of one of the three NTRK genes can lead to right treatment choices, as they show great benefit from TRK-inhibitory therapy. Nowadays, we start to recognize the histomorphology that in most cases correlates with the presence of the NTRK fusion in sarcomas. With our research, we aimed to broaden the diagnostic spectrum of this category and its correlation with the clinical and prognostic aspects. We described two soft tissue tumors with NTRK3 fusions among 70 soft tissue and bone sarcomas. Both are spindle cell neoplasm from the soft tissues with variable growth patterns, in accordance with prior publications. Pan-TRK immunohistochemistry was positive, and one of the cases displayed weak nuclear staining which correlated with the ETV6 fusion partner. In contrast to what has been described in literature, none of the tumors we present showed CD34 or S100-protein expression on immunohistochemistry. Moreover, we investigated the correlation of morphology and clinical behavior of these tumors. Namely, the neoplasm with the ETV6-NTRK3 fusion was superficial located and displayed an indolent course, in contrast to the published cases that display an aggressive behavior. Finally, we described an exceedingly rare TFG-NTRK3 – fused sarcoma with location in deep soft tissue that developed metastatic disease.

To conclude, NTRK-fused sarcomas are spindle cell tumors with variable growth patterns. Pan-TRK immunohistochemistry can pinpoint the cases that need further investigation by means of molecular testing. Nuclear positivity correlates with ETV6-NTRK3 fusion. According to our results, the presence of specific fusion partners do not seem to be a good surrogate marker to predict prognosis. Location of the tumor (superficial versus deep) may be an additional prognostic factor.

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

The studies involving human participants were reviewed and approved by Ethics Committee of the Antwerp University Hospital/University of Antwerp. Written informed consent for participation was not provided by the participants’ legal guardians/next of kin because: the study is retrospective and we used only historical samples for which additional informed consent from the patients was not needed.

AUTHOR CONTRIBUTIONS

Conceptualization, VS, PP; Formal analysis, VS; Funding acquisition, PP and ES; Investigation, VS, KW; Methodology, VS; Supervision, ES, PP and EM; Visualization, V.S.; Writing—original draft, VS; Writing—review and editing, VS, KW, KN, GS, PD, ES, EM. All authors have read and agreed to the published version of the manuscript.

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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