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Tenosynovial giant cell tumour: from active surveillance to surgery and systemic therapy

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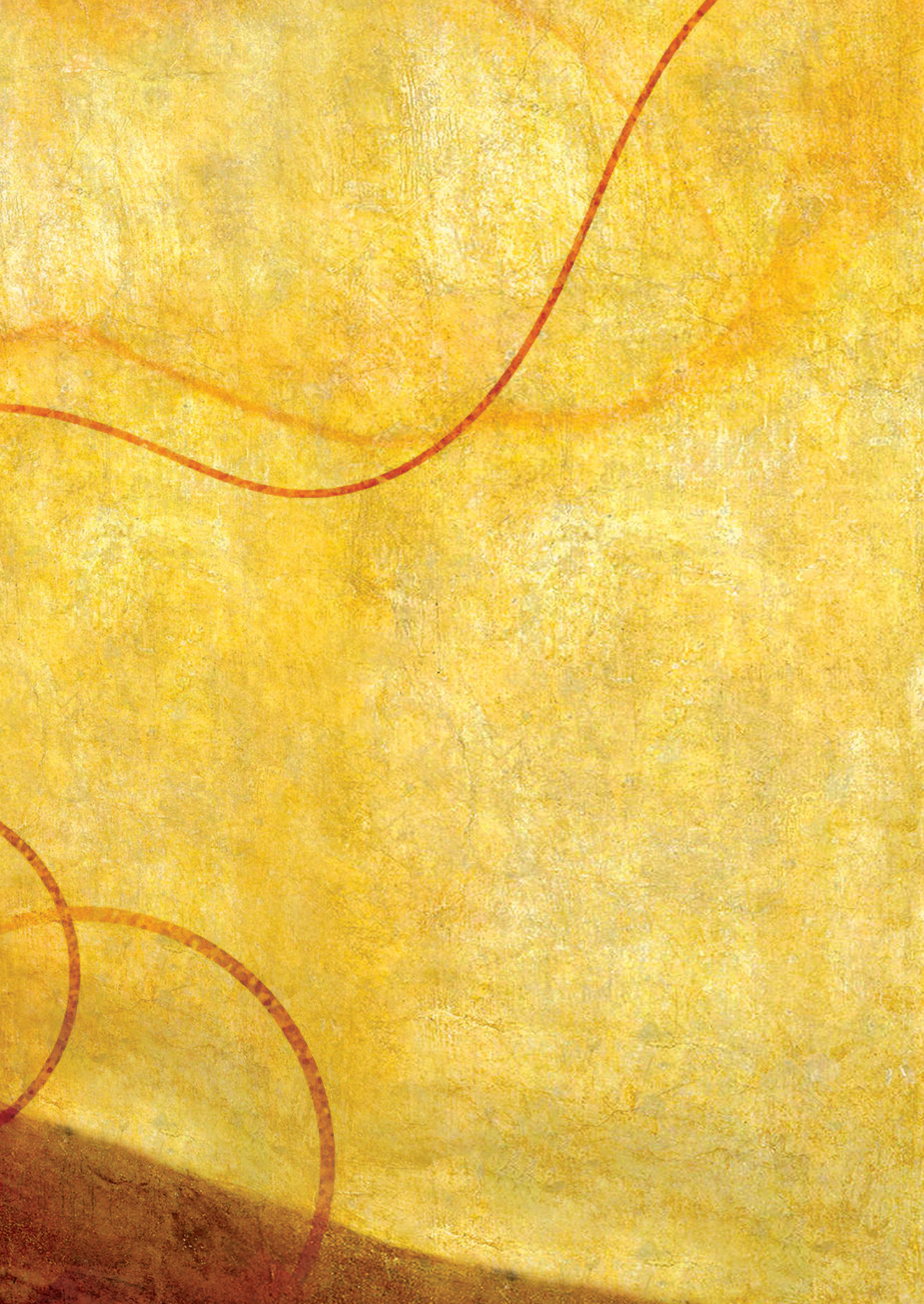
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Chapter 10

**Thesis summary, general discussion
and future perspectives**



This thesis investigated the journey of patients with diffuse-type Tenosynovial Giant Cell Tumour (TGCT), ranging from the onset of symptoms to the multidisciplinary treatment. This final chapter summarises the results and conclusions and discusses future perspectives.

Thesis summary

The following chapters shed light on the intricacies of TGCT, especially the diffuse-type (D-TGCT), and the efforts to understand and manage this rare neoplasm. **Chapter 2** introduces the Tenosynovial Giant Cell Tumour Observational Platform Project (TOPP), the first prospective disease registry involving 176 patients from multiple sarcoma centres in Europe and the United States (1). This study gained insight into the characteristics of D-TGCT by assessing the journey of these patients from disease onset to diagnosis, disease severity, treatment patterns, rate of recurrence and impact of the disease on patient-reported outcome measurements (PROMs). Also, the effect on health outcomes and economics was described. D-TGCT has its onset in a relatively young working population and may interfere highly with daily activities such as work (2). There is often a delay in diagnosis of multiple years and visits of several medical practitioners before receiving the proper diagnosis. With high recurrence rates and limited treatment options, the treatment of D-TGCT is complex and often based on the disease status and clinical expertise of the treating physician. Therefore, developing multidisciplinary guidelines is essential. Patients evaluated by multidisciplinary teams only sometimes require a change of treatment plan, as evidenced by the low rate of changing treatment strategy over the 2-year observational period (3).

As observed in Chapter 2, patients often experience a delay in diagnosis. Conventional radiographies often do not show abnormalities. Magnetic Resonance Imaging (MRI) is the imaging modality of choice to diagnose TGCT and evaluate disease severity (4, 5). **Chapter 3** describes the imaging characteristics of D-TGCT affecting the knee, including several differential diagnoses that can mimic D-TGCT. A structured report template is provided to scrutinise the knee's anterior, middle and posterior compartments and medial and lateral gutters (6). Also, the evaluation of tumour response on new systemic therapies is described. Finally, a first attempt was made at objective volumetric quantification of D-TGCT by 3D segmentation. Although this was a time-consuming and operator-dependent process, since all cases were segmented manually, automated volumetric quantification of tumour load will become more critical as systemic therapies evolve quickly (7).

Once D-TGCT is diagnosed, an adequate treatment plan is required. For symptomatic patients, surgery is still regarded the primary choice in treatment (8, 9). However, more information is needed about the natural course of D-TGCT and the effect of active

surveillance (10). **Chapter 4** analyses D-TGCT patients initially treated with active surveillance and its effect on the radiological and clinical course. This international, multicentre retrospective cohort included 61 therapy-naïve patients from eight sarcoma centres worldwide (11). During follow-up, 36% of the patients had radiological progression after a median of 21 months, and 18% of the patients who did not have osteoarthritis at baseline developed degenerative changes during follow-up. On the other hand, 64% did not clinically deteriorate, and only one third required subsequent treatment. Although follow-up time was limited and only a subset of the D-TGCT patients were included, active surveillance can be considered an acceptable initial approach for therapy-naïve patients. We recommend that active surveillance should only be initiated after MDT agreement and shared decision-making with the patient balancing clinical complaints and the risk of progression or joint degeneration.

The surgical treatment of TGCT was explored in more detail in the following three chapters.

Chapter 5 evaluates the management of TGCT in the foot and ankle, one of the most common soft-tissue tumours of the foot and ankle (12). It is the first large series describing multimodal treatment, including systemic therapies. This is the only chapter including treatment of localised-type TGCT (L-TGCT) since this type is common in the foot and ankle. Eighty-four patients were retrospectively included from two sarcoma centres in the Netherlands and the United Kingdom, of which 44 had L-TGCT and 40 D-TGCT (13). L-TGCT predominantly affects the forefoot, while D-TGCT involves more extensive areas of the foot and ankle. Where most L-TGCT cases can successfully be treated by surgery alone, recurrence rates were relatively high for D-TGCT (61%). Systemic therapies initially had good results in D-TGCT patients not amenable to surgery but progressed in 36% during follow-up, and patients often experienced significant side effects. We recommend that patients with D-TGCT or severe L-TGCT will benefit from multidisciplinary treatment involving specialised clinicians such as foot/ankle and sarcoma surgeons together with oncologists.

Although complete excision is regarded as the gold standard, this can be challenging due to D-TGCT's extensive growth. Sometimes, surgeons deliberately choose not to resect all tumourous tissue, or it may be impossible to remove all tumour since extensive surgeries are associated with iatrogenic morbidity. **Chapter 6** reports the largest cohort of surgically treated D-TGCT patients in one sarcoma centre. This study aimed to analyse the effect of surgical intention (complete/incomplete resection) and postoperative tumour presence on radiological and clinical outcomes. In 20 years, 144 patients with D-TGCT underwent surgery as primary treatment in one sarcoma centre, of which 125 were treated by isolated

open synovectomies (14). In 80%, surgeons intended to remove all tumour tissue. There was a median follow-up of 64 months. Both incomplete resections and the presence of postoperative remaining tumours were associated with significantly higher rates of radiological progression ($p=0.021$ and $p=0.001$, respectively). Furthermore, patients with postoperative tumour presence clinically worsened more frequently compared to patients without residual disease. Therefore, surgeons should aim for complete removal of D-TGCT balancing progressive disease and surgical sequelae. When complete removal of the tumour is not regarded feasible, one should consider other multimodal or neoadjuvant therapeutic strategies.

Chapter 7 is the last chapter investigating the surgical treatment of D-TGCT, especially the knee. D-TGCT is often located intra- and extra-articularly on both the anterior and posterior sides of the knee, requiring incisions from both sides (15-17). This study evaluated whether surgery on two sides of the knee should be performed in one or two stages and focused on postoperative short-term outcomes, such as achieved range of motion within one year after surgery, length of hospital stay and complications. In this international, multicentre, retrospective cohort study, 191 patients from nine sarcoma centres worldwide underwent a one- or two-stage synovectomy of the anterior and posterior side of the knee between 2000 and 2021 (18). Of these 191 patients, 117 underwent a one-stage synovectomy, and 74 a two-stage synovectomy. Patients undergoing a one-stage synovectomy did not experience impaired rehabilitation within one year after surgery, did not have more complications but had a shorter hospital stay (4 vs. 6 days, $p < 0.0001$). One stage synovectomy is therefore considered safe and efficient in the surgical treatment of TGCT about the knee.

After looking into surgical therapies in more detail, the last two chapters focus on systemic therapies. The interest in this treatment modality is growing, and they provide new options for patients not regarded amenable to surgery (7, 10).

Chapter 8 reviews disease mechanisms involved in TGCT, potential therapeutic targets and evaluates systemic therapies (19). The pathogenesis of TGCT is consistent apoptosis resistance, inflammation and matrix degradation. Although several pathways are involved in this pathogenesis, the most studied drug target is the Colony Stimulating Factor 1 (CSF1) – Colony Stimulating Factor 1 Receptor (CSF1R) axis due to the overexpression of CSF1 in TGCT patients. Different systemic therapies have been investigated, particularly CSF1-CSF1R targeted therapies, such as imatinib, emactuzumab, cabaralizumab, nilotinib, vimseltinib, and pexidartinib. Currently, only pexidartinib has been approved by the US Food and Drug Administration (20). The European Medicines Agency refused

market authorisation due to uncertainties on the risk-benefit ratio (21). Results are awaited of new therapies as there is an unmet need for broader availability of TGCT-related drugs.

Since CSF1R antagonists have only been studied in the last decade, data regarding their long-term efficacy still needs to be provided. Nevertheless, it is essential to know the long-term effects while TGCT has its onset in a young patient population. **Chapter 9** is the first study investigating the long-term effects of nilotinib in patients with advanced or relapsing D-TGCT. The study extends a previously conducted, multi-centre, open-label, single-arm, phase 2 clinical trial (ClinicalTrials.gov, NCT01261429) (22). Between 2010 and 2012, 56 patients were enrolled at 11 sarcoma centres. All patients received oral nilotinib twice daily until disease progression, intolerable toxicities, the patient's decision to withdraw or completion of one-year of treatment. This study analysed the long-term progression-free survival by retrospectively updating the investigator-assessed progression in 2021 (23). Of the 56 patients, 48 were included, with a median follow-up of 102 months. The median progression-free survival was 77 months, and the five-year progression-free survival was 53%. Twenty-seven (58%) received additional treatment. No unfavourable long-term effects were observed. This study demonstrated the mixed impact of nilotinib as several patients had ongoing disease control after limited treatment duration. In contrast, half of the patients had disease progression and required subsequent treatment.

General discussion & Future perspectives

Over the last two decades, the scientific interest in TGCT has been growing due to the druggable target CSF1R in TGCT (19). This led to a significant increase in research papers, and as a result, a consensus has been formed regarding treating L-TGCT (24). If symptomatic, this nodular tumour can be surgically removed with relatively low recurrence rates (25). However, treatment of D-TGCT remains open to discussion (10). Although D-TGCT is a benign tumour, it is likely to reoccur, can behave aggressively and can have a detrimental effect on the quality of life of young and active patients (26). Management of these non-malignant tumours can be complex, especially when they become chronic. Treatment may be required if patients experience symptoms, but not at any price. This thesis provided insight into the natural course of D-TGCT and the journey that patients undergo from disease onset into the diagnostic and heterogeneous treatment landscape. The goal was to create more disease awareness and to answer open questions regarding the optimal treatment strategy of D-TGCT.

In the past, a variety of names have been used for this family of lesions, such as pigmented villonodular synovitis, tenosynovial giant cell tumour of tendon sheath, synovial

xanthoma, synovial endothelioma, benign fibrous histiocytoma, amongst others (27). In 2013, the WHO established TGCT as an encompassing name, including the localised and diffuse subtypes (28). More recently, a group of sarcoma experts suggested changing the name of localised TGCT to nodular TGCT as it better reflects imaging and clinical findings (10). Besides, Tenosynovial Giant Cell Tumours also share the same abbreviation as Testicular Germ Cell Tumours (29). Continuously changing the nomenclature results in ambiguity, and it is recommended to be consistent in terminology to gain more awareness and disease familiarity (30). Furthermore, information regarding TGCT needs to be more accessible for health care practitioners and patients, and patient associations need to be promoted. This will lead to a decrease in diagnostic delays and referrals to the right healthcare professionals.

It is challenging to obtain substantial cohorts to address research questions for a rare disease with low incidence numbers, such as D-TGCT. This thesis set up multiple global collaborations between tertiary sarcoma centres to assemble meaningful research cohorts (2, 11, 13, 18). For example, the first prospective disease registry for D-TGCT (TGCT Observational Platform Project; TOPP) was conducted, and in this thesis, the first results of this prospective study were reported (2). Data was collected at set time points for two years. Setting up a prospective study for an orphan disease requires commitment, time, and often money, especially when a longer follow-up is desired. The downside of collaborations including only experienced tertiary sarcoma centres is that this possibly introduces selection bias by under-referral of less severe cases. On the other hand, the patient group with more severe or extensive tumour load is the most demanding in (surgical) management.

TOPP gave insight into the journey that D-TGCT patients undergo and showed that active surveillance is often regarded as the first treatment of choice, primarily for patients experiencing limited symptoms with subsequently less impact on their quality of life (2). This advocates that the disease burden drives shared treatment decision-making and that patient-based care is vital in this benign and often chronic disease. As a result, further research into the role of active surveillance in D-TGCT was performed in this thesis. In addition, TOPP demonstrated the demanding healthcare utilisation of D-TGCT, caused by multiple visits to physical therapists, medical specialists, hospitalisations, and rehabilitation, as well as social costs following work absence due to illness or even early retirement (2, 31).

Imaging

The clinical profile of D-TGCT is non-specific as is common in several joint diseases. MRI is the standard imaging modality to diagnose this disease as it shows characteristic imaging features (4, 32, 33). It is also helpful for preoperative mapping and assessment

of the response of systemic therapies (34, 35). MRI availability and quality are growing, making this modality more accessible. Assessing D-TGCT on MRI can be difficult, especially for those who do not often encounter this disease entity. Therefore, a structured report template is provided in this thesis (6). However, it is suggested that a dedicated (oncological) musculoskeletal radiologist should evaluate the MRIs due to the rarity and complexity of D-TGCT.

Other modalities, such as combinations of emission tomography and computed tomography, containing 18F-Fluorodeoxyglucose positron emission tomography, computed tomography (18F-FDG-PET/CT) or bone single-photon emission computed tomography (SPECT/CT), have been reported to show distinctive features of D-TGCT, helpful in diagnosing (36, 37). However, their added value compared to MRI needs to be demonstrated, and these modalities are more complex, less available and have higher costs and radiation exposure.

With a growing interest in systemic therapies, MRIs are more frequently utilised to evaluate their effect. The response to systemic therapies is mainly assessed by quantification of tumour volume. The Response Evaluation Criteria in Solid Tumours (RECIST 1.1 or modified-RECIST) is a general tool used to detect changes in tumour size (34). However, D-TGCT's irregular shape, asymmetrical growth and lack of clear margins make RECIST unsuitable. More recently, Peterfy et al. developed a specific D-TGCT tool called tumour volume score (TVS) (35). TVS defines the tumour size relative to the joint size. It's a semiquantitative tool, and as clinicians have to estimate the percentage of tumour volume, it will introduce intra- and inter-observer variability.

Additionally, TVS still needs to be validated as a method for response assessment. This illustrates the need for automated volumetric quantification of D-TGCT on MRI. In this thesis, the first approach was made into 3D segmentation, allowing the quantification of the tumour volume objectively. Although 3D segmentation objectively measures the volume instead of estimating, the segmentations were performed manually and were thus operator-dependent. Automatic segmentation by deep learning has already been developed for knee synovitis (38). But developing automatic segmentation of D-TGCT has yet to be accomplished.

The severity of D-TGCT is not only based on tumour volume. Assessment of D-TGCT should also include other findings, such as inflammation, cartilage invasion, bone erosions, muscular, tendinous, ligament and neurovascular involvement (5). Finally, objective findings on MRI need to be correlated to PROMs, as a decrease in tumour volume does not always correspond to an improvement in PROMs and vice versa (14).

Treatment

The treatment armamentarium of D-TGCT is broad. Most patients are treated by surgery, as shown in TOPP, including different surgical approaches (3). D-TGCT is a heterogeneous tumour and ranges from a small intra-articular lesion to a widespread tumour located intra- and extra-articular (39). Specific surgical themes were addressed in this thesis to aid in treatment decision-making. Unfortunately, due to the retrospective character, these studies were performed without predefined radiological outcome measurements. In this thesis, we demonstrated that there is often residual tumour after surgery on MRI (14). Therefore, assessing radiographic outcomes in a standardised fashion can increase the reliability of future studies. On the other hand, the necessity of MRIs as part of standard follow-up is questionable. With a benign nature, QoL should be the main treatment goal and perhaps MRIs should only be performed on clinical indication.

When patient and surgeon decide that surgery is indicated, surgeons should pursue a complete macroscopic resection to achieve better outcomes in tumour control (14). Additionally, most tumours can be removed in one session without negatively impacting joint function, and patients have to rehabilitate only once (18). But if D-TGCT is located intra- and extra-articular, complete resection may not be feasible or may not be desirable, as extensive surgery can lead to joint damage or postoperative stiffness. In these cases, one should be cautious about planning only tumour debulking or primary irradical resection; and other treatment modalities should be considered.

An issue not addressed in this thesis is the choice of open or arthroscopic synovectomies. Although most surgeries were performed open in our studies, some experts allege for arthroscopic surgery (40-43). The advantages of arthroscopy are better visualisation of tumours, especially intra-articular, and hypothesised better functional outcomes. On the other hand, it can be challenging to access extra-articular tumour extend located in specific compartments and gutters, resulting in incomplete resection. Open surgery may provide a better overview and access to the tumour, but extensive open surgery can lead to iatrogenic morbidity. A meta-analysis by Chandra et al. estimated a 1.56 increased risk of recurrence after arthroscopic surgical management of D-TGCTs of the knee compared to an open approach (43). Contrarily, a recent case series showed promising results using posterior and trans-septal portals (44). Collaborations between oncological orthopaedic surgeons and skilled arthroscopic orthopaedic surgeons could improve oncological outcomes and can provide a solution when extensive open surgery is too morbid.

It remains difficult to determine which surgical approach provides the best outcomes due to the heterogeneity of D-TGCT disease extent and localisation, patient population and prior treatments. Therefore, individually tailored treatment is required. Besides surgery,

other modalities should be looked at, especially considering the high recurrence rates following surgery (9). Since D-TGCT is a non-life-threatening disease, a wait-and-see approach can be an option for patients whose current disease burden is acceptable and for whom surgical treatment could deteriorate complaints and does not outweigh the risk for progression (2, 3). Many patients do not clinically worsen during a follow-up of more than two years; some even improve and require no further treatment (11). Although active surveillance was only studied as primary treatment for patients included in this thesis, TOPP has demonstrated that this approach is also common and suitable for patients who underwent prior treatment (2). The majority remained on no treatment at the end of TOPP, although it is unknown if they remain without treatment after longer follow-up (3).

The role of radiotherapy as a stand-alone or (neo)adjuvant treatment remains disputed. Some studies have reported positive radiotherapy results, but their low-level quality limits these studies (45, 46). As D-TGCT is a non-malignant disease affecting a young patient population, the risk of radiation-induced malignant transformation is regarded unacceptable (47). Also, radiotherapy may cause complications such as fibrosis, joint stiffness or secondary osteoarthritis (48). However, the incidence of these adverse effects are considered very low, especially in low-dose radiation. Furthermore, these adverse effects have not been reported in more recent studies with a relatively long follow-up (49-51). With the development of systemic therapies, the role of radiotherapy seems to disappear into the background. Still, radiotherapy could be considered in selected cases such as patients who do not tolerate systemic therapies.

Since the first successful report of imatinib in a patient with D-TGCT, the interest in systemic therapies has grown rapidly (52, 53). It can provide an alternative treatment solution for patients not amenable to surgery. Several drugs have been developed and tested, where the majority of drugs focus on the inhibition of CSF1R, amongst others (19). Nevertheless, only one drug has been approved for the treatment of TGCT, namely pexidartinib, and this is only available in a couple of countries (20). In 2020, the European Medicines Agency refused market authorisation due to an unfavourable risk-benefit ratio (21). Only slight improvement in symptoms and joint function were observed, but hepatotoxicity occurred as adverse event in a few cases. (54) The Food and Drug Administration encountered this by mandating the risk evaluation management system (REMS) program (55). Furthermore, it was not clear how long the effect of pexidartinib lasted. Because systemic therapy developments for D-TGCT are relatively new, data regarding the long-term effects still need to become available in the near future. This is of utmost importance as D-TGCT affects a young patient population. A few studies, one of which is in this thesis, have shown that long-term tumour control can be achieved and that no new complications occur later on (23, 56-59). Approval of drugs for ultrarare

diseases can be challenging. When research organisations collaborate, it will be easier to set up randomised controlled trials, which may lead to accelerated drug approval (60, 61).

Most recently developed TGCT related drugs are tyrosine kinase inhibitors (TKIs). Pexidartinib was developed with stronger selective activity against CSF1R than prior TKIs. Although expected to result in fewer adverse events than non-selective CSF1R inhibitors, they still occurred (34). While D-TGCT is a benign disease, there is less urgency to eradicate the tumour and accept side effects against all costs compared to malignancies. Vimseletinib is a switch-control TKI designed explicitly with greater selectivity for CSF1R and not inhibiting closely related kinases, expected to cause less adverse events (62). The first results of a phase 1 and 2 study showed that vimseletinib was well tolerated and had a manageable safety profile (63). The results of a randomised, controlled phase 3 trial are still awaited (ClinicalTrials.gov, NCT05059262).

Intra-articular injections provide another pharmacotherapeutic option to enable high drug concentration at the tumour site while minimising systemic exposure and toxicity. Meaningful clinical improvement in function and quality of life were seen after 12 weeks in a pilot study where patients received a selective anti-CSF1R monoclonal antibody (64). The results of a phase 2 study are still awaited (ClinicalTrials.gov, NCT04731675). The local and systemic effect of administering a high dose of CSF1R inhibitor locally is not known yet.

Besides developing a drug with an optimal risk/benefit ratio, the usage of TGCT-related drugs needs to be further elucidated. There is still much unknown, such as the ideal length of treatment duration and the effect of intermittent treatment (56, 65, 66). Also, the effect of systemic therapy in combination with surgery requires further assessment (67). In cases with extensive tumour growth, systemic therapy might reduce tumour load so that complete resection can be performed resulting in better outcome of surgery. In contrast, in cases of incomplete resection, systemic therapies can target the residual disease and thus reduce the number and recurrences and elongate time to recurrence.

Recent translational research by IJzerdoorn et al. demonstrated that the neoplastic cells of TGCT lack an autocrine loop involving CSF1-CSF1R (68). This suggests that current CSF1-CSF1R inhibitors do not target the neoplastic cells but mainly affect bystander activated macrophages. However, the authors state that they cannot entirely exclude the possibility of CSF1R expression on neoplastic cells in rare cases. Additionally, they found expression of platelet-derived growth factor receptor (PDGFR) on neoplastic cells. Imatinib targets PDGFR and could, therefore, possibly target both the neoplastic cells

and bystander macrophages. Nonetheless, previous studies researching imatinib showed that several patients do not benefit from treatment with imatinib (56, 69).

Conclusion

The broad clinical spectrum of D-TGCT, varying from an asymptomatic indolent tumour to a locally aggressive tumour with high potential of recurrence, means that every patient's journey is unique. Treatments range from wait-and-see to surgery or systemic therapy (2). Treatment decisions are not necessarily right or wrong and should be individually tailored. Shared treatment decision-making is crucial to balance decreasing symptoms and improving function and quality of life on the one hand and obtaining tumour control and preventing/stopping further joint degeneration on the other hand. Due to the heterogeneity in clinical presentation, the multimodal treatment and conundrum in the order of treatment options, patients will benefit from care centralised in specialised sarcoma centres (70, 71).

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