




CLINICAL ARTICLE

A New Simple and Practical Clinical Classification for Tenosynovial Giant Cell Tumors of the Knee

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Objective: To propose a simple and practical clinical classification for tenosynovial giant cell tumor (TGCT) of the knee.

Methods: A retrospective study was conducted to verify the value and significance of this clinical classification. TGCT growth patterns, knee joint capsule, and bone erosion were applied to establish this novel clinical classification. Seventy-eight patients who underwent surgery for TGCT from 2008 to 2016 were identified. This novel clinical classification was retrospectively applied to patients' existing classification, and patients with different TGCT types were statistically compared to verify the significance of the clinical classification.

Results: The clinical classification included three types and four subtypes. Type 1: localized TGCT, Subtype 1a: localized intra-articular TGCT, Subtype 1b: localized extra-articular TGCT. Type 2: diffuse TGCT, Subtype 2a: diffuse intra-articular TGCT with bone normal, Subtype 2b: diffuse intra-articular TGCT with bone destruction. Type 3: diffuse TGCT across the knee joint capsule. The mean follow-up time for the 78 patients was 59.6 months. Twenty-one patients were in Subtype 1a, four were Subtype 1b, 38 were Subtype 2a, seven were Subtype 2b, and eight were Type 3. Oncological results and surgical complications differed significantly ($P = 0.000$, $P = 0.000$). The mean Musculoskeletal Tumor Society functional scores differed significantly at 27.8 for Type 1 patients, 22.9 for Type 2 patients, and 17.0 for Type 3 patients ($P = 0.000$).

Conclusions: This clinical classification can be easily used to evaluate TGCT of all knees prior to surgery or other treatments and can help determine surgical options.

Key words: Clinical classification; Knee; Pigmented villonodular synovitis; Surgery; Tenosynovial giant cell tumor

Introduction

Tenosynovial giant cell tumors (TGCT), previously known as pigmented villonodular synovitis, are locally aggressive neoplasms composed of synovial-like mononuclear cells mixed with multinuclear giant cells, foam cells, siderophages, and inflammatory cells, which may be intra-articular or extra-articular¹. According to the World Health Organization Classification of Tumors of Soft Tissue and Bone, 5th ed. (2020), TGCT can be classified by their location and growth patterns as localized or diffuse¹. One study reported

that the incidence rates per million person-years were 30.3 for localized types and 8.4 for diffuse types in Denmark². TGCT may occur at any age but usually occurs between the ages of 30 and 50 years, with a slight predominance in women²⁻⁴. Although TGCT can occur in any joint, it is more common in the knee, and in more than 75% of cases it develops within the intra-articular portion of the knee^{2,3,5}.

At present, the treatment strategies for patients with both localized and diffuse types of TGCT remain controversial. Treatment options include open surgical synovectomy,

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arthroscopic resection, radiosynovectomy, external-beam radiotherapy, cryosurgery, targeted therapy, immunotherapy, arthroplasty, and amputation^{2-4,6-17}. Although many treatments have been reported, the extensively accepted treatment for TGCT of the knees is surgical resection. Tumor recurrence is the most common complication related to tumor resection, and recurrence rates are reported to be as high as 50% for some patients¹³. Complete resection is an important treatment option for TGCT resection but is difficult to perform in some patients with TGCT in the knees because of the cruciate ligaments and without sacrificing other tissues. Maintaining a balance between retaining the knee structure and removing the TGCT with negative margins is difficult. Because the tumor is rare and non-life-threatening, clinical evidence regarding TGCT in the knees is lacking. Previously published studies on TGCT have mainly focused on uncommon tumor location case reports or surgical methods and results^{6,15,18-22}. Only one paper reports a severity classification of TGCT on magnetic resonance imaging (MRI)²³. This classification is not specific to knee TGCT, and complex classification makes clinical use difficult. The guidance that surgeons can obtain from the literature is limited.

At present, no specific clinical classification of TGCT of the knee exists for determining treatment options. Surgical treatment for TGCT is not definitive for every patient because it involves a high risk for local recurrent disease and a relatively high risk for postoperative complications⁴. The aims of this study include: (i) to analyze clinical characteristics of TGCT in the knee; (ii) to propose a clinical classification for TGCT of the knee which will be useful for determining surgical treatment strategies; and (iii) to verify the clinical value of this novel clinical classification.

Materials and Methods

Inclusion and Exclusion

In this retrospective study, patients with TGCT of the knee received treatments at the 960th Hospital of the PLA Joint Logistics Support Force and Tianjin Hospital from January 2008 to January 2016. Patients who met the following criteria were eligible for this study: (i) pathological diagnosis of TGCT was definite; (ii) TGCT involved the knees; and (iii) surgery was performed on the TGCT. The exclusion criteria included the following: (i) pathologically malignant TGCT or pulmonary metastasis during treatment and follow-up; (ii) incomplete clinical, radiographic, and pathological records; and (iii) no standardized follow-up data.

Classification Basis

After discussion within the study group, it was finally decided to classify using three aspects. This process was assisted by imaging and pathology experts. Three reference indicators were applied to establish this novel clinical classification. Magnetic resonance imaging (MRI) acquisition was performed on an MR discovery 750 3.0-T scanner (GE Medical Systems, Milwaukee, WI, USA) using a

dedicated 16-channel knee coil. All patients underwent general assessment and knee TGCT examination before treatments. Imaging included preoperative X-ray, computed tomography (CT), and MRI.

TGCT, Localized or Diffuse

First, the TGCT growth patterns, including localized and diffuse types, were important to tumor resection methods and prognoses.

Knee Joint Capsule

Second, the knee joint capsule was considered an important barrier for joint tumors. Differences existed in the treatments between intra-articular and extra-articular TGCT.

Bone Erosion

Third, bone erosion was an important reference indicator for establishing this classification. Bone destruction reflected tumor hyperplasia and determined the surgical method.

Surgical Treatments

For patients with TGCT of the knee, surgical resection methods included arthroscopic tumor resection, single-incision tumor resection under open vision, tumor resection *via* anterior and posterior approaches, tumor reduction, tumor resection and total knee arthroplasty, and tumor resection and bone defect reconstruction.

Tumor Recurrence

All patients accepted postoperative follow-up. The discovery of tumor in the same location by postoperative imaging evaluation was considered as tumor recurrence.

MSTS Scoring

The MSTS 93 score had been used for functional evaluation at the last follow-up in our study. Each of these six variables, including pain, function, emotional acceptance, and supports for walking ability and gait, were assessed on a 5-point scale, giving a maximum score of 30 points. Higher MSTS score signifies better functional results.

Complication

The clinical complications, such as functional limitation, infection, pain, and swelling were recorded. Oncological failure was not recorded as a complication.

Ethical Approval

Ethical approval was granted by the Institutional Ethical Committee of the 960th Hospital of the PLA Joint Logistics Support Force, and patient consent was also obtained for this study. The research was carried out according to the principles set out in the Declaration of Helsinki (1964) and all subsequent revisions.

Statistical Analysis

In this study, the SPSS 13.0 (Chicago, IL, USA) statistical software was used for data analysis. All patient analysis was conducted with regard to tumor type, resection methods, complications, and functional outcomes. First, the following descriptive statistics were calculated: frequency, percent, mean, and standard deviation. Thereafter, comparisons were performed using Student's t-test for continuous variables and Pearson's chi square test/Fisher's exact test for categorical variables. The level of statistical significance was set at $P < 0.05$.

Results

General Results

Clinical data for 78 patients with TGCT of the knee were summarized. The series included 23 men and 55 women, with a mean age of 43.0 years (range, 16–74 years). The mean follow-up period was 59.6 months (range, 24–132 months).

Surgical Treatments

Half of the patients underwent knee arthroscopic minimally invasive tumor resection, and the other half underwent open tumor resection. Among the open surgery patients, 21 patients underwent single-incision tumor resection, 13 patients underwent combined anterior posterior approach, and five patients underwent tumor resection and total knee arthroplasty (TKA).

Tumor Recurrence

In this series, 52 patients did not have postoperative recurrence in the follow-up, and 26 patients had postoperative tumor recurrence.

MSTS Scoring

The mean MSTS score of postoperative limb function in 78 patients was 23.8, ranging from 10 to 30.

Complication

Twenty-three patients had limited knee function and activity after operation. Pain and swelling were very common for recurrent patients, and 21 patients had corresponding symptoms. Extensive ankyloses of the knee were found in two of these patients.

Novel Clinical Classification for TGCT of the Knee

Based on each patient's TGCT preoperative imaging and intraoperative examination, three types and four subtypes of knee TGCT were identified and classified: Type 1: localized TGCT, Subtype 1a: localized intra-articular TGCT, Subtype 1b: localized extra-articular TGCT. Type 2: diffuse TGCT, Subtype 2a: diffuse intra-articular TGCT with bone normal, Subtype 2b: diffuse intra-articular TGCT with bone destruction. Type 3: diffuse TGCT across the knee joint capsule. Table 1 lists the classifications, and Fig. 1 characterizes the

TABLE 1 A novel clinical classification of TGCT in the knee

Type	Description
Ia	Localized, intra-articular TGCT
Ib	Localized, extra-articular
Ila	Diffuse, intra-articular
Ilb	Diffuse, intra-articular, bone destruction
III	Diffuse, across the knee joint capsule

MRI performances. Using this novel clinical classification for TGCT of the knee, 21 patients were Subtype 1a, four were Subtype 1b, 38 were Subtype 2a, seven were Subtype 2b, and eight were Type 3.

For Subtype 1a patients, five underwent tumor resection under open vision, while the other 16 underwent arthroscopic tumor resection (Fig. 2). No differences were found in tumor recurrence or postoperative limb function between the two surgical types, but small wounds and rapid recovery occurred with arthroscopic tumor resection. Four patients with Subtype 1b whose TGCT was outside of the knee joint capsule underwent tumor resection under open vision. Immobilizing the knee was unnecessary, no tumor recurrence was found, and postoperative limb function was normal. For the 38 patients with Subtype 2a, 23 underwent arthroscopic resection with less complete tumor resection tampering with anterior incision for complete resection, 12 underwent anterior incision, and three underwent anterior and posterior surgical removal of the TGCT. Nineteen patients experienced postoperative TGCT recurrence with swelling and pain. For the seven patients with Subtype 2b, three underwent total knee arthroplasty after TGCT resection, and four underwent anterior and posterior surgical removal of the TGCT without arthroplasty. Two patients experienced postoperative TGCT recurrence after tumor resection while no patients experienced recurrence after total knee arthroplasty. For the eight patients with Type 3 TGCT, complete resection of the TGCT was nearly impossible. Six patients underwent TGCT resection with anterior and posterior approaches, while two underwent total knee arthroplasty. One patient who accepted total knee arthroplasty experienced postoperative infection. Five patients had postoperative TGCT recurrence, and two of these underwent repeat tumor resection. One patient underwent bone defect reconstruction with bone cementation because of severe bone destruction with unbearable pain (Fig. 3).

Statistical Analyses of the Three Types

Twenty-five patients were Type 1, 45 patients were Type 2, and eight patients were Type 3 (Table 2). On average, Type 1 patients were younger, and the difference was statistically significant ($F = 3.731$, $P = 0.029$). Women were predominantly in Types 1 and 2, while more men than women were Type 3, these differences were significant ($\chi^2 = 6.651$, $P = 0.036$). Follow-up duration did not differ significantly between the groups ($F = 1.915$, $P = 0.154$). Among Type

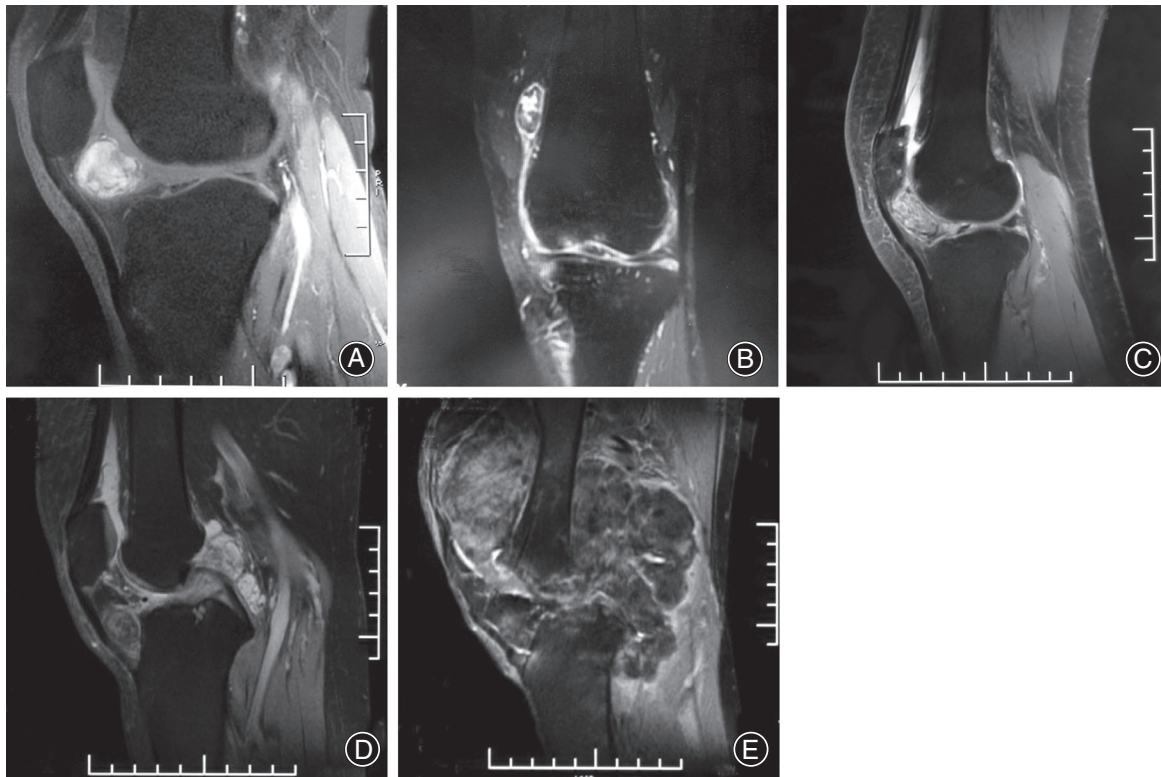


Fig. 1 Preoperative MRI examinations of patients with TGCT of the knee identified three types and four subtypes of knee TGCT as follows. (A): Subtype 1a, localized intra-articular TGCT. (B): Subtype 1b, localized extra-articular TGCT. (C): Subtype 2a, diffuse intra-articular TGCT with bone normal. (D): Subtype 2b, diffuse intra-articular TGCT with bone destruction. (E): Type 3, diffuse TGCT across the knee joint capsule.

1 patient, no patients experienced recurrence, three developed limited knee function, and two developed pain or swelling. Among Type 2 patients, 21 developed tumor recurrence, 18 developed limited knee function, and 14 developed pain or swelling. Among Type 3 patients, five developed tumor recurrence, two developed limited knee function, and five developed pain or swelling. Oncological results and surgical complications differed significantly ($\chi^2 = 19.163$, $P = 0.000$, and $\chi^2 = 23.321$, $P = 0.000$, respectively). The mean Musculoskeletal Tumor Society (MSTS) functional scores differed significantly at 27.8 for Type 1, 22.9 for Type 2, and 17.0 for Type 3 patients ($F = 43.552$, $P = 0.000$).

Discussion

Clinical Characteristics of TGCT in the Knee

It is undeniable that surgery is still the main treatment for TGCT. There is a lack of consensus on which technique should be used, and when²⁴. In this series, minimally invasive resection and open resection accounted for half of these patients, respectively. Tumor recurrences and postoperative complications were common. It is always difficult to choose different treatment methods for different patients, although there are many studies on surgical methods of TGCT^{3,8,13,17}. For localized TGCT, arthroscopic resection and open surgery

can achieve good tumor control, and arthroscopic surgery should be recommended with less trauma. For diffuse-type TGCT, the surgical method is controversial. It is difficult to achieve a balance between complete tumor resection and preservation of knee function. TKA after tumor complete resection could enable regaining acceptable knee function. TKA combined with synovectomy was considered an effective treatment for advanced TGCT with degenerative lesions²⁵. However, compared with patients with osteoarthritis who underwent total knee arthroplasty, patients with diffuse TGCT experienced more surgical complications, including stiffness and infection¹⁵. A systematic review makes conclusions that arthroscopic excision is effective in minimizing morbidity and surgery-related complications, while an open surgical technique provides a more successful resection with a lower incidence of local recurrence²⁴. They cannot conclude with confidence which of the surgical techniques is better at stopping a progression towards osteoarthritis and the need for TKA²⁴. Surgical treatment for knee TGCT remains challenging because no clinical classifications or graded treatment strategies are currently available.

Radiosynoviorthesis is reported to be an effective adjuvant therapy for patients after total synovectomy because total synovectomy leaves no visible diseased tissue, which increases the risk of local recurrence^{7,26}. However,

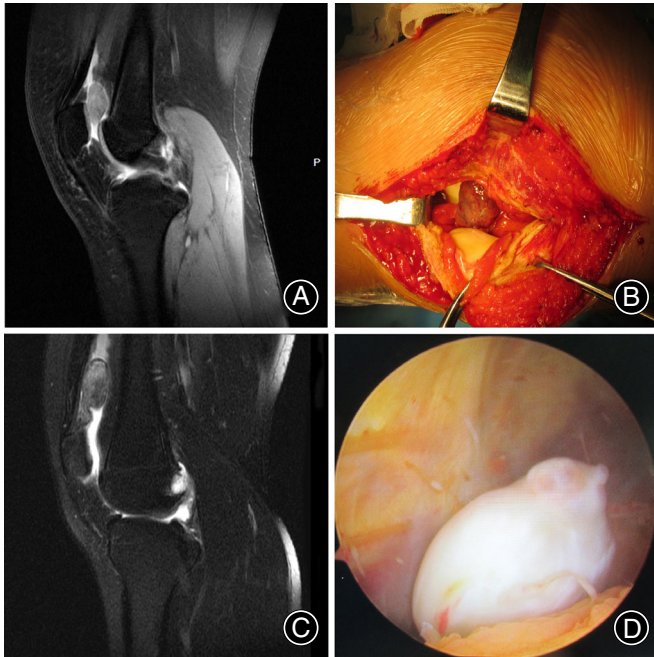


Fig. 2 Two patients with similar TGCT MRI performances were classified as Subtype 1a (A, C). One patient underwent tumor resection under open vision (B), while the other patient underwent arthroscopic tumor resection (D).

complications have also been reported after radiosynoviorthesis²⁷. Because colony-stimulating factor 1 gene expression was elevated in most TGCT cases, structure-guided blockade of colony-stimulating factor 1 receptor kinase has been used to treat TGCT, resulting in a prolonged regression in tumor volume in most patients^{9,14}. Pexidartinib

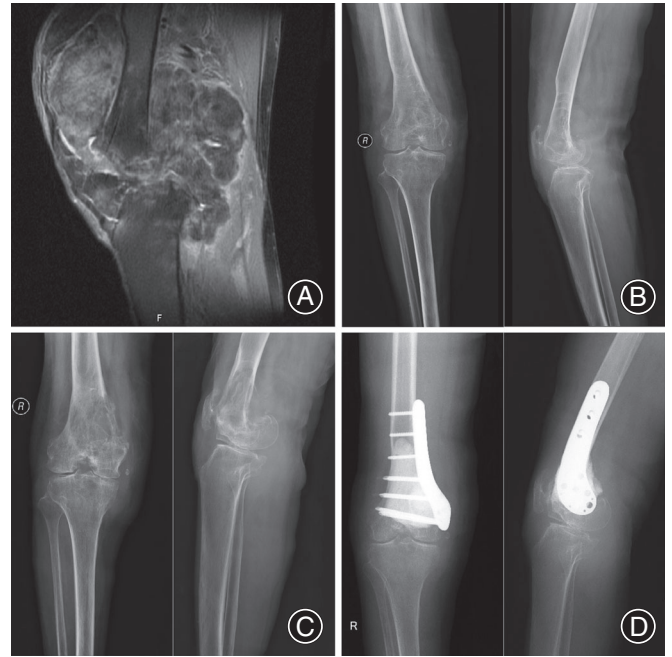


Fig. 3 One patient with Type 3 TGCT underwent tumor resection with an anterior and posterior approach. Preoperative MRI (A) and preoperative X-rays (B) showed a large tumor volume and partial bone erosion. Ten months after TGCT resection, this patient returned to the hospital with unbearable pain. X-rays (C) showed severe bone erosion. This patient underwent TGCT resection and bone defect reconstruction with bone cementation (D).

provides a novel non-surgical treatment option for patients with tenosynovial giant cell tumor^{28,29}. Systemic therapy may be valuable as part of a multidisciplinary approach³⁰.

TABLE 2 The statistic analyses of 78 tenosynovial giant cell tumors in the knee joints

Categories	Type 1*	Type 2*	Type 3*	Total	Statistical value	P
Number, n(%)	25 (32.1)	45 (57.7)	8 (10.3)	78 (100)		—
Age, year, means(SD)	38.3 (12.6)	43.5 (16.2)	54.6 (12.1)	43.0 (15.3)	$F = 3.731$	0.029
Sex, n(%)					$\chi^2 = 6.651$	0.036
Male	9 (36.0)	9 (20.0)	5 (62.5)	23 (29.5)		
Female	16 (64.0)	36 (80.0)	3 (37.5)	55 (70.5)		
Follow-up, months, means(SD)	58.8 (30.4)	56.5 (29.1)	79.4 (38.4)	59.6 (30.9)	$F = 1.915$	0.154
Surgery, n(%)					$\chi^2 = 9.982$	0.007
Arthroscopy	16 (64.0)	23 (51.1)	0 (0)	39 (50.0)		
Resection	9 (36.0)	22 (48.9)	8 (100)	39 (50.0)		
Recurrence, n(%)					$\chi^2 = 19.163$	0.000
Exist	0 (0)	21 (46.7)	5 (62.5)	26 (33.3)		
None	25 (100)	24 (53.3)	3 (37.5)	52 (66.7)		
Complication, n(%)					$\chi^2 = 23.321$	0.000
Functional limitation	3 (12.0)	18 (40.0)	2 (25.0)	23 (29.5)		
Pain or swelling	2 (8.0)	14 (31.1)	5 (62.5)	21 (26.9)		
None	20 (80.0)	13 (28.9)	1 (12.5)	34 (43.6)		
MSTS, means(SD)	27.8 (1.7)	22.9 (2.9)	17.0 (6.0)	23.8 (4.4)	$F = 43.552$	0.000

* According to this new classification of TGCT in knees.

A New Clinical Classification for TGCT of the Knee

To our knowledge, this is the first specific clinical classification of TGCT of the knee for guiding clinical treatments. MRI examinations of the knee are often used to make diagnoses and treatment decisions because of their high sensitivity, specificity, and diagnostic accuracy³¹⁻³³. In this study, we proposed a new, simple, and easy-to-use clinical classification of TGCT based on MRI, which divides all TGCT of the knees into three types and four subtypes. In Type 1, or localized TGCT, the tumor can be controlled and knee function can be gained *via* simple resection. Surgeons should pursue a small surgical wound and rapid postoperative recovery. Arthroscopic tumor resection is recommended for patients with localized TGCT in the knee capsule (Subtype 1a), while direct tumor resection is recommended for those with localized TGCT outside the knee capsule (Subtype 1b).

Bone invasion by TGCT is less common but has a reported incidence rate of 27%⁴. Thus, the classification of diffuse TGCT of the knee capsule includes two subtypes. Complete tumor resection with one incision or combined anterior and posterior incisions is recommended for patients with diffuse TGCT without bone invasion (Subtype 2a). Complete tumor resection of the soft tissue and bone is recommended for patients with diffuse TGCT in the knee capsule with bone invasion (Subtype 2b). In this series, approximately one in two patients with Type 2 had postoperative tumor recurrence, and knee stiffness was the most common surgical complication. TKA after tumor complete resection could enable regaining acceptable knee function.

Patients with diffuse TGCT spanning both the inside and outside of the knee capsule (Type 3) had extra-articular lesions that were always accompanied by lesions in the intra-articular compartments⁸. Complete tumor resection was nearly impossible to accomplish because pathological tissue was often spread widely throughout the joint and was difficult to access and remove. Neoadjuvant or adjuvant therapies should be recommended for these patients because of the

high risk of recurrence after surgery alone. In this series, one in two patients with Type 3 TGCT who underwent TKA experienced tumor recurrence and joint infection. TKA should be chosen cautiously, and clinicians should inform patients of the necessary surgical risks during preoperative communication.

Verify the Clinical Value

In order to verify the practicability and effectiveness of classification, we retrospectively analyzed the previous cases and classified 78 patients with knee TGCT. The results showed that all patients could be easily divided into various types, which preliminarily confirmed the practical value of this classification. Because it is a retrospective analysis, there are some differences between the surgical methods and the classification treatment guidance. The clinical guidance value of classification needs to be verified by further prospective clinical studies.

Nevertheless, in the retrospective analysis of cases, we can still see that there are many differences in the treatment methods between different types. For patients with Type 1, about one-third of the patients underwent open surgery while the other patients underwent minimally invasive surgery. The postoperative follow-up showed that there was no recurrence. Therefore, in classifying clinical guidance, it is recommended that Subtype 1a patients undergo minimally invasive surgery to reduce iatrogenic trauma. For patients with Types 2 and 3 TGCT, arthroscopic synovectomy of the TGCT is not recommended because complete resection of the TGCT *via* arthroscopy is difficult. Although the technique of knee arthroscopy is more mature^{34,35}, there is still a blind area for complete resection of tumor under arthroscopy. Lower recurrence rates have been reported for open synovectomy (average 14%, maximum 67%) than for arthroscopic synovectomy (average 40%, maximum 92%) in patients with diffuse TGCT³⁶. Some patients underwent a combined open posterior and anterior synovectomy, which

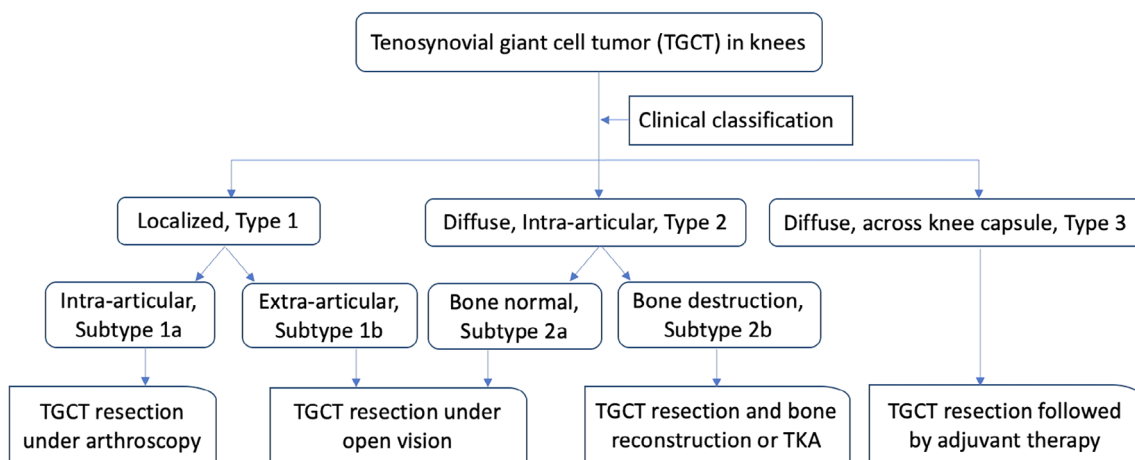


Fig. 4 Recommended treatment process for TGCT of the knee.

was recommended because it allowed excellent visualization and removal of the intra-articular and extra-articular TGCT¹⁶. Limitations in postoperative knee function were common. Patients with TGCT of the knees should be clinically classified before treatment because different surgical treatments are recommended for different types and subtypes (Fig. 4).

Research Limitations

This study had some limitations. First, this new clinical classification of TGCT of the knee is based on MRI evaluation and distinguishing between Types 2a and 2b can sometimes be difficult. Different clinicians may obtain different results and reach different conclusions. Treatment principles do not differ significantly between patients with Subtypes 2a and 2b, and the TGCT should be completely removed. The difference is that Subtype 2b patients with severe bone destruction should undergo bone reconstruction or TKA. The classification is easier for patients who show severe bone destruction *via* MRI. Second, the number of patients used to evaluate this classification was small, which makes it difficult to make definitive statements regarding the differences in recurrences, complications, and postoperative function among the different types without a large-sample statistical analysis. Third, this new classification was proposed in theory; thus, and it should be further tested and continually modified. This classification is suitable for bone tumor surgeons and bone tumor imaging doctors with certain clinical experience.

Maybe, it is difficult for medical workers who are new to this field to use and understand.

In conclusion, based on each patient's TGCT preoperative imaging and intraoperative examination, three types and four subtypes of knee TGCT were identified and classified: Type 1: localized TGCT, Subtype 1a: localized intra-articular TGCT, Subtype 1b: localized extra-articular TGCT. Type 2: diffuse TGCT, Subtype 2a: diffuse intra-articular TGCT with bone normal, Subtype 2b: diffuse intra-articular TGCT with bone destruction, Type 3: diffuse TGCT across the knee joint capsule. Arthroscopic tumor resection is recommended for TGCT with Subtype 1a, while direct tumor resection is recommended for TGCT with Subtype 1b. The TGCT with Subtypes 2a and 2b should be completely removed while TKA is recommended for some patients with severe bone destruction in Subtypes 2b. Neoadjuvant or adjuvant therapies should be recommended for TGCT with Type 3.

Consent

The written informed consent was obtained from the patient for publication of this report and any accompanying images.

Authors' Contributions

XY, YH, KZ carried out the studies, participated in collecting data, and help to draft the manuscript. KZ performed the data analysis, participated in its design, and drafted the manuscript. MX, JZ, HC conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

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