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# Clinical and immunohistochemical analysis of diffuse tenosynovial giant cell tumour of the temporomandibular joint

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*Abstract.* The objective of this study was to summarize diagnostic points and treatment strategies for diffuse tenosynovial giant cell tumours (D-TSGCTs) of the temporomandibular joint (TMJ), and to evaluate the expression of proteins related to bone destruction and recurrence. The clinical and histopathological characteristics of 24 cases were analysed retrospectively. TRAP staining and immunohistochemical staining for MMP-9, MMP-13, and Ki-67 were performed. The median age of the patients was 45.5 years; the female to male ratio was 1.7:1. In 11 cases (45.8%), skull base destruction seen on computed tomography was confirmed by surgery. Computer-assisted navigation was performed in six cases. Four patients received adjuvant radiotherapy after first surgery. Five patients had recurrent lesions. Multinucleated giant cells were positive for TRAP, MMP-9, and MMP-13. The average Ki-67 index of the recurrent cases was significantly higher than that of the non-recurrent ones ($P < 0.05$). This study demonstrates the aggressive and recurrent nature of D-TSGCT occurring in the TMJ. Computer-assisted navigation is helpful to protect vital structures and determine margins. Adjuvant postoperative radiotherapy is recommended for local control of residual or recurrent tumour. In conclusion, MMP-9 and MMP-13 may play a role in bone destruction of D-TSGCT, and the Ki-67 index has predictive significance for recurrence.

Key words: diffuse tenosynovial giant cell tumour; temporomandibular joint; matrix metalloproteinase; TRAP; Ki-67.

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Diffuse tenosynovial giant cell tumour (D-TSGCT), also known as pigmented villonodular synovitis (PVNS), is a lesion deriving from the synovial membranes of joints, bursae, and tendon sheaths[1]. In 1941, Jaffe et al.[2] first described PVNS occurring in the large joints. In 2013, PVNS and D-TSGCT were classified as the same lesion by the World Health Organization[3]. The exact aetiology of D-TSGCT is still controversial. Currently, reports of cytogenetic abnormalities, such

 

as gene fusion involving *CSF1* (1p13) and *COL6A3* (2q35)[4], as well as aneuploid DNA[5] and malignant potential, have suggested that D-TSGCT is a neoplastic lesion rather than an inflammatory process[6]. Other possible aetiologies involve repetitive trauma, disturbances of lipid metabolism, and haemorrhage[7].

D-TSGCT commonly occurs in the joints of extremities, especially in the knee[6]. The common clinical presentations are pain, swelling, haemorrhagic effusion, and joint stiffness in the large joints. The bone destruction rate of D-TSGCT involving the knee joint is about 50%[8]. Surgical intervention, such as open synovectomy and arthroscopy, are the main therapy approaches. The recurrence rate in the large joints is 18–50%[9].

D-TSGCT of the temporomandibular joint (TMJ) is relatively rare. About 130 cases had been reported in the English language literature as of 2018. D-TSGCT involving the TMJ is easily misdiagnosed as a parotid neoplasm, ear disease, or other temporomandibular tumour, due to its non-specific clinical symptoms. The mass can cause damage to the joint structures, and the skull base can even be destroyed in severe cases; about one-third of cases described in the literature have involved destruction of the skull base[10,11]. The mechanism of bone destruction remains unclear, although Darling[12] observed that bone destruction was related to matrix metalloproteinases (MMPs) in the knee.

In the present study, a retrospective analysis of the clinical and histopathological characteristics of 24 patients with D-TSGCT of the TMJ was performed in order to share our experiences in the diagnosis of this tumour and the treatment strategies applied. Tartrate-resistant acid phosphatase (TRAP) staining and immunohistochemical staining for MMP-9 and MMP-13 were performed to explore the mechanism of bone destruction. The expression of Ki-67, which is a nuclear protein related to proliferative activity, was also explored.

## Patients and methods

This retrospective study included 24 cases of histologically confirmed D-TSGCT. The patients with D-TSGCT attended the Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, between January 2008 and September 2017. The patients' demographic characteristics, clinical and imaging features (magnetic resonance imaging (MRI) or computed tomography scans (CT)), histological characteristics, treatment strategies, and prognoses were summarized and analysed. The results were expressed as median values or percentages. Three-dimensional reconstruction was based on contrast-enhanced CT scanning. Surgical planning and intraoperative navigation were performed using Brainlab iPlan software (Brainlab AG, Munich, Germany) in six cases.

Pathological specimens were fixed in 10% formalin solution and embedded in paraffin. Immunohistochemistry staining was performed on sections 4-μm thick using the Elivision technique. Heat-mediated antigen retrieval was performed using ethylenediaminetetraacetic acid (EDTA) buffer (pH 8.0). Rabbit monoclonal antibody to MMP-9 (1:150; OriGene, Beijing, China) and Ki-67 (1:100, OriGene, Beijing) and mouse monoclonal antibody to MMP-13 (1:150, OriGene, Beijing) were used as primary antibodies; these were incubated with tissue sections at 4 °C overnight. Negative controls involved replacement of the primary antibody with antibody diluent. The Ki-67 index refers to the percentage of Ki-67-positive cells among all cells in five random high-power views. The average Ki-67 index of different groups was compared using the *t*-test, with a significant test level of 0.05. All data were analysed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA).

The acid phosphatase kit (Sigma, USA) was used for TRAP staining. Sections were dewaxed and hydrated. Deionized water was pre-warmed to 37. Reactive solution was prepared according to the manufacturer's protocol and placed in a 37 water bath. The sections were incubated in the prepared solution for 1 hour in a 37 water bath protected from light, and then counterstained with haematoxylin for 2 minutes.

## Results

### Clinical and imaging characteristics

The age at disease onset ranged from 24 to 62 years (median 45.5 years) and the female to male ratio was 1.7:1. Common symptoms included swelling, limited mandibular movement, arthralgia, and mandibular deviation. Two cases had otitis media and hearing loss.

Bone erosion, mostly involving the temporal bone, followed by the condyle, sphenoid bone, and posterior wall of the maxillary sinus, was found in 91.7% of cases (22/24). Of note, 45.8% (11/24) of cases showed destruction of the skull base through the glenoid fossa of the temporal bone or greater wing of the sphenoid bone. The two cases with otitis media and hearing loss showed a soft tissue shadow emerging into the mastoid sinus and tympanum. Contrast-enhanced CT showed diffuse or peripheral post-contrast enhancement in all 17 cases (Fig. 1A). On MRI, which was available for 16 cases, these nodular or lobulated masses exhibited heterogeneous signal intensity (predominantly hypointensity to isointensity), both on T1-weighted imaging and T2-weighted imaging (Fig. 2). Six cases were diagnosed preoperatively as D-TSGCT by core needle biopsy guided by ultrasound or computer-assisted navigation. Before this, three cases had been suspicious for a low-grade malignant tumour or even sarcoma due to the aggressive behaviour presenting on CT. In eight cases, fine needle biopsy was performed at another hospital and the results suggested mesenchymal tumours with giant cells in six cases, a low-grade malignant tumour in one case, and a salivary gland tumour in one case. Intraoperative frozen section diagnosis was performed for all patients.

All patients underwent open surgery under general anaesthesia. Computer-assisted navigation was performed in six cases extending to the skull base or infratemporal fossa (Fig. 1B–D). A temporal craniotomy was performed in five cases with intracranial extensions, in collaboration with neurosurgeons. The dura was intact in all cases with skull base destruction. In four cases with extension into the infratemporal fossa and parapharyngeal space, lower lip incision and mandibular osteotomies were performed.

Due to skull base destruction with unclear margins, four patients received postoperative radiotherapy to control residual tumours with a dose range of 44–55 Gy 1 to 3 months after the first surgery, and no progression was observed on MRI. Follow-up ranged from 18 to 134 months. Five cases (22.7%) were suspicious for recurrence on MRI. One recurrent tumour was controlled by external radiotherapy alone, with no progression for 8 years. Two patients underwent a second surgery (Fig. 2) and the remaining two patients without clinical symptoms required conservative follow-up.

### Histopathology

Grossly, the tumours appeared friable and brownish. Some lesions were accompanied by grey–white tough fragments suspicious for cartilaginous or osseous components. Two cases demonstrated cyst-like change. Microscopically, the

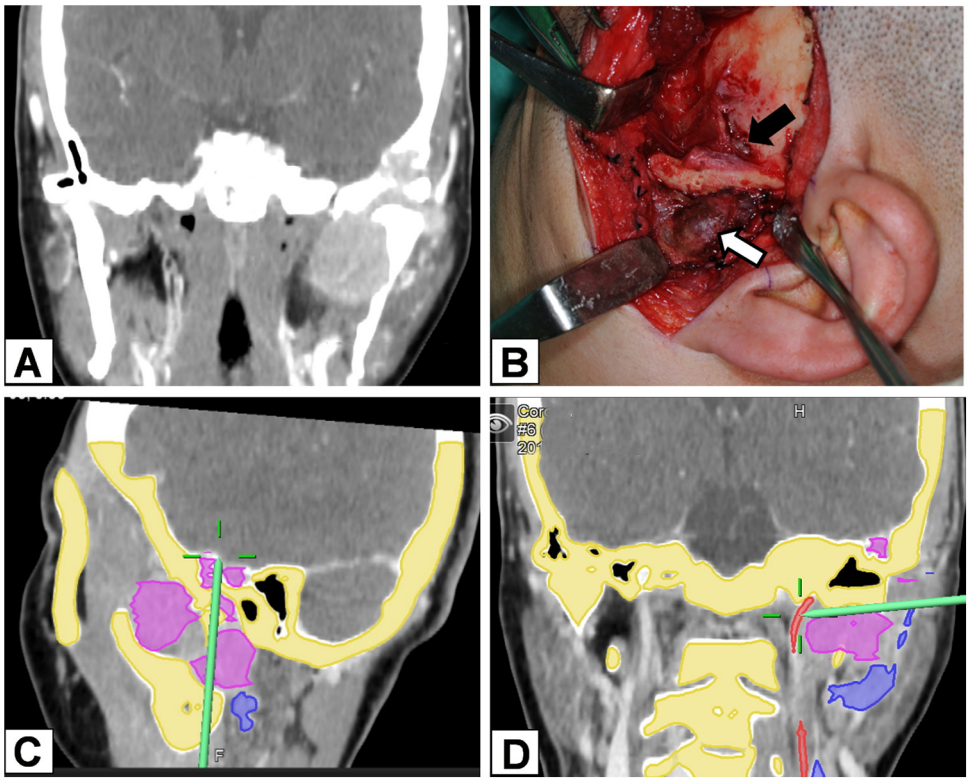


*Fig. 1.* A case of diffuse tenosynovial giant cell tumour involving the left TMJ in a 35-year-old woman. (A) CT scan showing a contrast-enhancing lesion surrounding the condyle with destruction of the skull base. (B) A brownish lesion (white arrow) with destruction of the temporal bone (black arrow) was exposed through the pre-auricular approach. (C) Determination of skull base margins to protect the dura by computer-assisted navigation. (D) Protection of the internal carotid artery by computer-assisted navigation.

tumours were mainly composed of mononuclear cells with scattered osteoclast-like multinucleated giant cells, foam-like cells, inflammatory cells, and hemosiderin deposition (Fig. 3). Thirteen cases contained varying degrees of chondroid metaplasia. The histological patterns of chondroid matrix included chondro-osseous, hyaline-like and lace-like calcification. The cytological features of monocytes were variable. The predominant smaller mononuclear cells containing palely eosinophilic cytoplasm were ovoid or spindle-shaped, and grooves of nuclei were occasionally visible. Larger mononuclear cells contained abundant eosinophilic cytoplasm, sometimes with ring-like hemosiderin deposition. The nuclei were round or oval, commonly with vesicular chromatin. The cytoplasm of some cells resembling xanthoma cells or foam cells was vacuolar. Multinucleated giant cells, which varied in quantity among cases, were polygonal or slender, with 3 to 50 nuclei. In the area of stromal fibrosis, the cells were often spindle-shaped and fibroblast-like. Fresh haemorrhagic cavities surrounded by macrophage-like cells containing hemosiderin were visible in some tumours.

### Immunohistochemistry and TRAP staining

MMP-9 and MMP-13 were mainly located in the cytoplasm, but were also present in small quantities in the extracellular matrix. Ki-67 was localized to the cell nucleus. The osteoclast-like multinucleated giant cells were strongly positive for TRAP, MMP-9, and MMP-13, and negative for Ki-67 (Figs. 4 and 5). The monocytes located in calcified areas were negative for Ki-67 as well. About 2% of monocytes showed strongly positive staining for MMP-9, MMP-13, and TRAP (Fig. 4). These monocytes were large and partially scattered around the multinucleated giant cells. The average Ki-67 index differed significantly between the recurrent cases and the non-recurrent ones ($P < 0.05$) (Fig. 5). There was no significant difference between the cases with skull base destruction and those without this destruction ($P > 0.05$) (Table 1).

## Discussion

This study is novel in reporting a large retrospective analysis of D-TSGCT of the TMJ. The main clinical symptoms of D-TSGCT in the TMJ are painful or painless masses around the joint with associated joint dysfunction. Otological symptoms, such as hearing loss and tinnitus, may present when the tympanum and temporal mastoid are involved. Patients may feel headache and nausea in a few cases if there is severe intracranial extension or even invasion of the cerebral parenchyma, as in one case reported by Son et al.[13].

The diagnosis is challenging because of the non-specific symptoms. CT clearly shows the extent of bone destruction. The typical hypointensity related to hemosiderin deposition in both T1-weighted and T2-weighted MRI is a preferable method for diagnosis and follow-up[14,15]. Another notable feature is that most cases show post-contrast enhancement on contrast-enhanced CT[16,17] or MRI[18], and the abundant blood supply in D-TSGCT has been observed by angiography by some researchers[19].

D-TSGCT with chondroid metaplasia is a rare subset of D-TSGCT, but it occurs relatively frequently in the TMJ[20]. Chondroid metaplasia was observed microscopically in 13 cases in the present study. Calcified chondroid metaplasia appeared as a patchy or spotty high-density area on

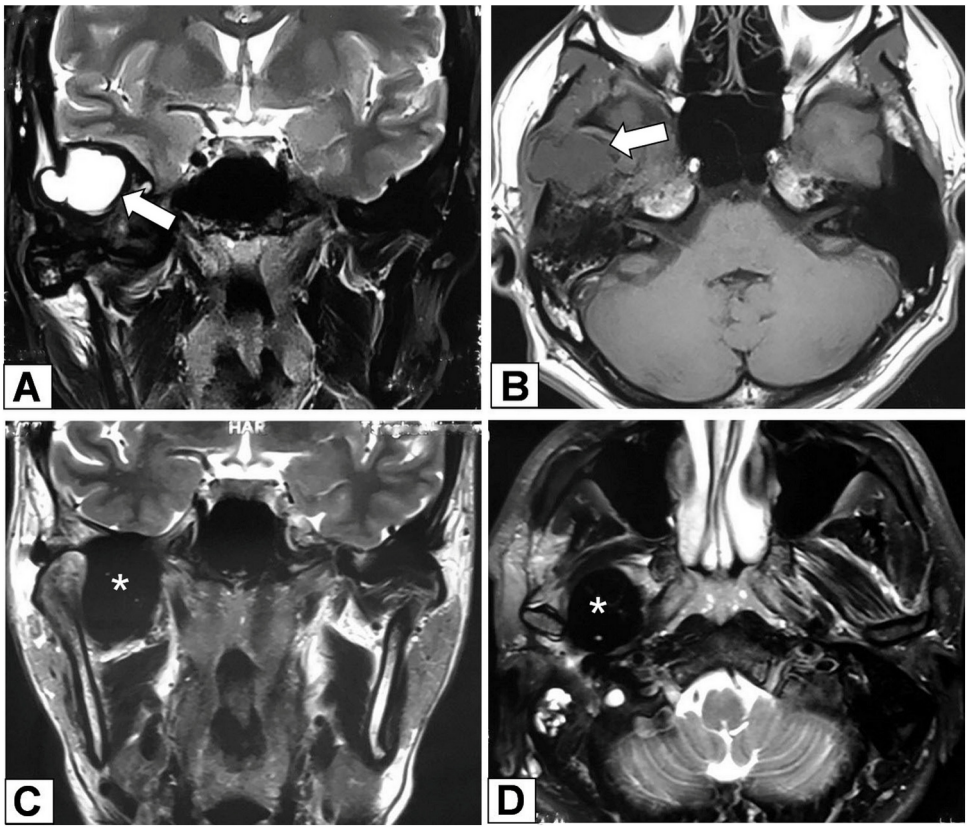


*Fig. 2*. MRI images of a recurrent diffuse tenosynovial giant cell tumour involving the right TMJ in a 27-year-old man. Images of the primary tumour revealing a predominant hypointense lesion with local cyst-like changes (white arrow) on T2-weighted imaging (A) and T1-weighted imaging (B). A recurrent hypointense lesion (white asterisk) was observed on T2-weighted imaging (C) and T2-weighted imaging (D) 10 months later.

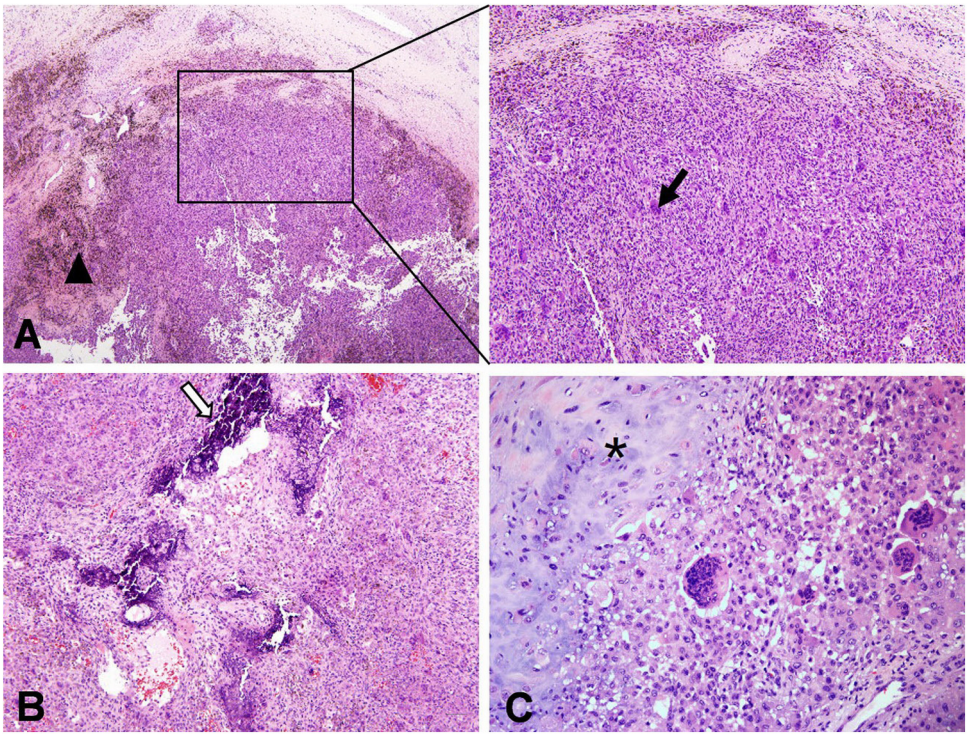


*Fig. 3*. Photomicrographs of haematoxylin and eosin staining. (A) Hemosiderin (black triangle) and multinucleated giant cells (black arrow) (original magnification ×40). (B) Calcification (white arrow, original magnification ×100). (C) Hyaline cartilage (black asterisk, original magnification ×400).

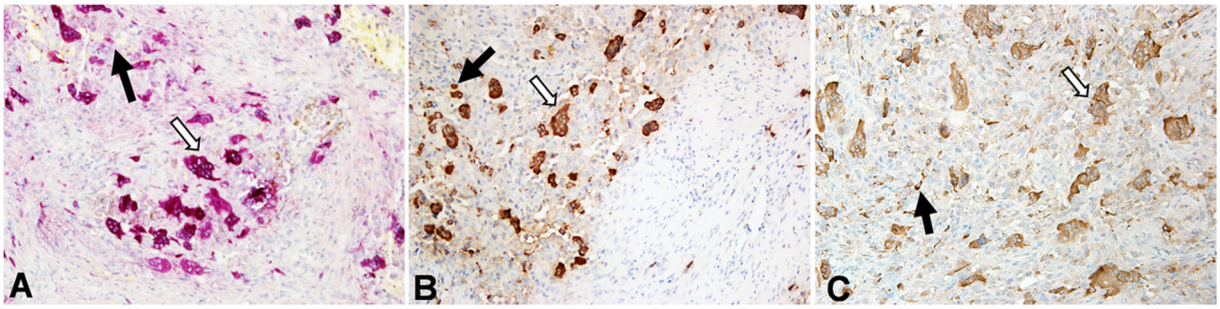


*Fig. 4*. TRAP staining and immunohistochemical staining (original magnification ×200). Multinucleated giant cells (white arrow) and some larger monocytes (black arrow) were positive for TRAP (A), MMP-9 (B), and MMP-13 (C).

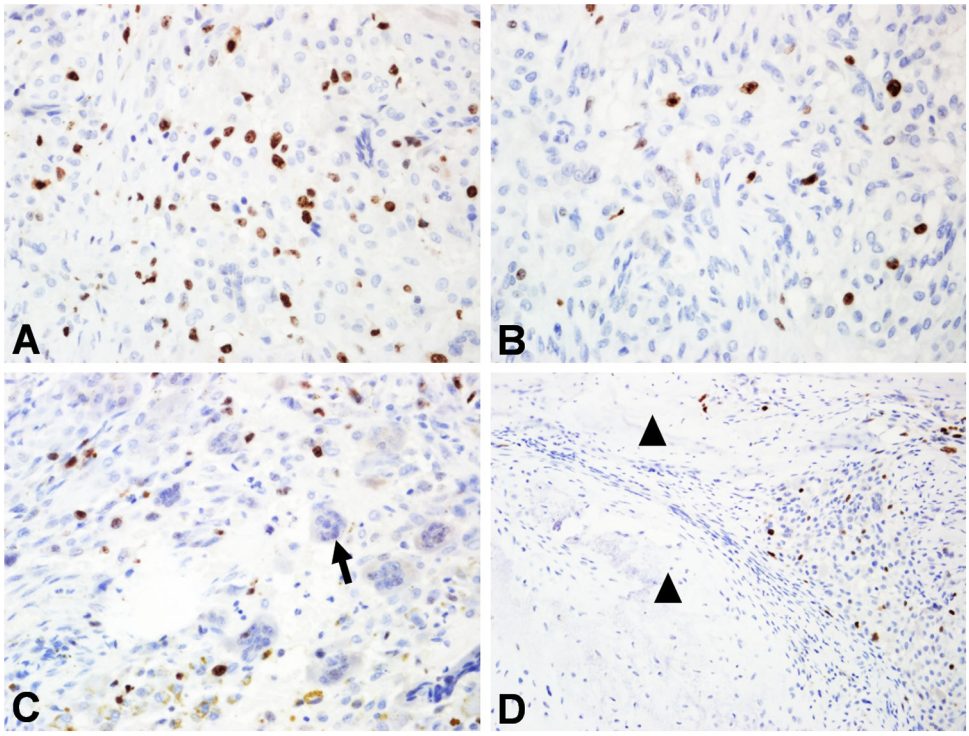


*Fig. 5*. Immunohistochemical expression of Ki-67 in diffuse tenosynovial giant cell tumour (original magnification ×400). (A) A recurrent case. (B) A non-recurrent case. (C) The multinucleated giant cells were negative for Ki-67. (D) The cells in calcified areas were negative for Ki-67.

*Table 1*. The Ki-67 index of 24 cases of diffuse tenosynovial giant cell tumour of the TMJ.

| Characteristic | Ki-67 index | | | *P*-value |
|---|---|---|---|---|
| | Range | Average | SD | |
| Recurrent | 9–10% | 9% | 0.5% | 0.04* |
| Non-recurrent | 2–11% | 6% | 2.7% | |
| Skull base destruction | 4–10% | 8% | 2.5% | 0.88 |
| No skull base destruction | 2–11% | 7% | 2.7% | |

TMJ, temporomandibular joint; SD, standard deviation.
* $P < 0.05$.

CT. It is important to recognize this phenomenon and differentiate D-TSGCT with metaplasia from other cartilage-forming tumours, such as synovial chondromatosis. Compared with D-TSGCT, synovial chondromatosis typically shows a large amount of effusion with enlargement of the capsule, and multiple small ring-like or tubular signals on MRI[21]. When malignant tumours cannot be excluded by imaging, ultrasound or navigation-guided core needle biopsies are recommended to enable correct diagnosis before surgery.

Surgical resection is still the main treatment strategy for D-TSGCT[11]. The recurrence rate in the TMJ with 5-year follow-up is 29%[22]. Postoperative complications include malocclusion, limitation of mouth-opening, mandibular deviation, and facial nerve palsy. Computer-assisted surgical navigation is helpful to protect the vital structures and determine margins when the tumour involves the skull base or internal carotid artery[23].

Complete resection of the lesion is required to prevent recurrence. However, a small amount of residual tumour may remain because of the need to prevent damage to the vital structures and preserve joint function when the tumour is adjacent to the internal carotid artery and dura. Adjuvant low-dose external-beam radiotherapy has been shown to be effective for postoperative local control of residual or recurrent tumour, for an inoperable tumour, and for a patient who was unwilling to undergo further surgery[24]. Transient radioactive stomatitis, itchiness or erythema of the local skin, and local hair loss after radiotherapy were observed in the present study and in some previous studies[25]. Long-term follow-up is suggested. Arthroscopic surgeries can be used for intra-articular lesions of the TMJ[26].

In recent years, tyrosine kinase inhibitors (nilotinib, imatinib, and PLX3397), which target the colony-stimulating factor 1 receptor, have been tested in clinical trials and have demonstrated clear efficacy. However, these drugs are still recommended only for advanced cases[27]. Intra-articular injection of Yttrium-90 was found to be effective with subtotal synovectomy, but a few cases with unacceptable local tissue necrosis have also been reported[28]. The safe dose and a full evaluation of the therapeutic efficacy of these adjuvant therapies still require further investigation, including multi-centre, large-sample trials.

Aggressive D-TSGCT can destroy bone. In the present study, the rates of osseous erosion and skull base destruction were 91.7% and 45.8%, respectively. The mechanism of bone destruction in D-TSGCT remains unclear. Osteoclasts fused of mononuclear/macrophage lineage precursor cells are the main cells that promote bone destruction. TRAP, a metallophosphatase, is a marker of osteoclasts, and it participates in bone resorption by osteoclasts[29]. In the present study, multinucleated giant cells were TRAP-positive, which indicates that these cells have an osteoclast phenotype. Similarly, some monocytes were positive. Anazawa et al.[30], in an electron microscopy examination study, found that some D-TSGCT monocytes contained many mitochondria, rough endoplasmic reticulum, and Golgi apparatus, similar to osteoclasts. Based on the above findings, it is speculated that the TRAP-positive monocytes in D-TSGCT are precursor cells of osteoclasts. TRAP-positive multinucleated giant cells and monocytes are related to bone destruction in D-TSGCT.

MMPs secreted by osteoclasts are responsible for osteoclast migration through collagen degradation[31] and bone resorption[32]. MMP inhibitors can inhibit bone resorption by osteoclasts[33]. MMPs are members of the zinc metalloproteinase family and can degrade most proteins in extracellular matrix, as well as in the basement membrane. Many studies have shown that MMPs are associated with tumour invasion and metastasis[34]. MMP-13 can degrade type I collagen, which accounts for 90% of the extracellular matrix collagen of bone. MMP-9 can degrade type IV collagen in the basement membrane and extracellular matrix. In the present study, MMP-9 and MMP-13 were strongly positive in osteoclast-like multinucleated giant cells and some monocytes. These findings indicate that MMP-9 and MMP-13 may play a role in tumour invasion and bone destruction in D-TSGCT.

Ki-67 is a nuclear protein associated with proliferative activity. The absence of Ki-67 expression in osteoclast-like multinucleated giant cells and monocytes located in calcified areas indicates that they are poorly proliferative. Berger et al.[35] found that the Ki-67 index of diffuse TSGCT in knee joints was higher than that for localized TSGCT. Mahendra et al.[36] found that the Ki-67 proliferation index was higher in PVNS than in haemorrhagic synovitis of the knee joints. In the present study, the average Ki-67 index of patients with recurrence was higher than that of patients without recurrence. These results imply that the Ki-67 index has predictive significance for recurrence of D-TSGCT, and that cases with a higher Ki-67 index need close follow-up. However, this conclusion needs to be verified in larger samples and with further follow-up.

In conclusion, D-TSGCTs occurring in the TMJ are relatively rare. This study demonstrates the aggressive and recurrent nature of D-TSGCT occurring in the TMJ. Hypointensity on MRI and post-contrast enhancement on contrast-enhanced CT or MRI are helpful for diagnosis. Computer-assisted navigation in surgical intervention is helpful to protect the vital structures and determine margins. The use of adjuvant postoperative radiotherapy is suggested for local control of residual or recurrent tumours, and long-term follow-up is recommended. Finally, MMP-9 and MMP-13 may play a role in bone destruction in D-TSGCT, and the Ki-67 index has predictive significance for recurrence.

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## Competing interests

The authors have no conflicts of interest.

## Ethical approval

Ethical approval was obtained from the Biomedical Institutional Review Board of Peking University School and Hospital of Stomatology (PKUSSIRB-201837088).

## Patient consent

Written consent was obtained from the patients to publish the photographs.

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