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Diagnostik und Therapie der Pigmentierten Villonodulären Synovitis (Riesenzelltumor der Sehnenscheiden)

Dissertation

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Carl Ferdinand Capellen

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Hiermit versichere ich, Carl Ferdinand Capellen, an Eides statt, dass ich die vorliegende Dissertation “Diagnostik und Therapie der Pigmentierten Villonodulären Synovitis (Riesenzelltumor der Sehnenscheiden)” selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Bottighofen, den 14.01.2020 / Bottighofen, 14.01.2020

Carl Ferdinand Capellen

Unterschrift / signature

Inhaltsverzeichnis

1. Abkürzungsverzeichnis

PVNS / PVS	Pigmentierte villonoduläre Synovialitis
RSO	Radiosynoviorthese
CSF1	colony stimulating factor 1
CSF1R	colony stimulating factor 1 receptor
VEGF	Vascular Endothelial Growth Factor
t(1;2)	Translokation von Chromosom 1 und 2
LR	Lokalrezidiv
MRT	Magnetresonanztomographie
CT	Computertomographie

2. Publikationsliste

2.1. Veröffentlichung I

Capellen CF, Tiling R, Klein A, Baur-Melnyk A, Knösel T, Birkenmaier C, Roeder F, Jansson V, Dürr HR. Lowering the recurrence rate in pigmented villonodular synovitis: A series of 120 resections. Rheumatology (Oxford). 2018 Aug 1;57(8):1448-1452. doi: 10.1093/rheumatology/key133

2.2. Veröffentlichung II

Dürr HR, **Capellen CF**, Klein A, Baur-Melnyk A, Birkenmaier C, Jansson V, Tiling R. The effects of radiosynoviorthesis in pigmented villonodular synovitis of the knee**.** Arch Orthop Trauma Surg. 2018 Dec 11. doi: 10.1007/s00402-018-3097-4.

2.3. Vorträge

Capellen C.F., Tiling R., Klein A., Baur-Melnyk A., Knösel, T., Jansson V., Dürr H.R.: Ergebnisse der Therapie der pigmentierten villonodulären Synovitis (PVS). Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU) 28.10.2016, Berlin.

Alexander Klein, **Carl F. Capellen**, Reinhold Tilling, Andrea Baur-Melnyk, Thomas Knösel, Volkmar Jansson, Hans Roland Dürr: Pigmented Villonodular Synovitis (Giant-cell Tumor of Tendon Sheath) Results of Surgical and Adjuvant Therapy. International Society of Limb Salvage (ISOLS), 12.05.2017, Kanazawa, Japan.

Capellen C.F., Tiling R., Klein A., Baur-Melnyk A., Knösel T., Jansson V., Dürr H.R.: Pigmented Villonodular Synovitis (Giant-Cell Tumor of Tendon Sheath) results of surgical and adjuvant therapy EMSOS 2016, 27./28.05.2016, La Baule, Frankreich.

2.4. Weiteres

Eingegangen mit den untersuchten Fällen in eine große internationale Sammelstudie:

Mastboom MJL, Palmerini E, Verspoor FGM, Rueten-Budde AJ, Stacchiotti S, Staals EL, Schaap GR, Jutte PC, Aston W, Gelderblom H, Leithner A, Dammerer D, Takeuchi A, Thio Q, Niu X, Wunder JS; TGCT Study Group, van de Sande MAJ. Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. Lancet Oncol. 2019 Jun;20(6):877-886. doi: 10.1016/S1470-2045(19)30100-7. Epub 2019 Apr 24.

Mastboom MJL, Staals EL, Verspoor FGM, Rueten-Budde AJ, Stacchiotti S, Palmerini E, Schaap GR, Jutte PC, Aston W, Leithner A, Dammerer D, Takeuchi A, Thio Q, Niu X, Wunder JS, van de Sande MAJ; Tenosynovial Giant Cell Tumors (TGCT) Study Group. Surgical Treatment of Localized-Type Tenosynovial Giant Cell Tumors of Large Joints: A Study Based on a Multicenter-Pooled Database of 31 International Sarcoma Centers. J Bone Joint Surg Am. 2019 Jul 17;101(14):1309-1318

3. **Einleitung und Grundlagen**

Das Krankheitsbild der Pigmentierten villonodulären Synovialitis (PVNS), definiert (WHO) als Riesenzelltumor der Sehnenscheiden oder tenosynovialer Riesenzelltumor stellt eine sehr seltene aber gutartige, neoplastische Proliferation der Membrana synovialis ausgehend von Sehnenscheiden, Gelenkkapseln oder ganz selten auch von Schleimbeuteln (Bursen) dar.
Erstmals beschrieben wurde eine lokale, noduläre Variante der Erkrankung 1852 von Chassaignac an einer Flexorsehne der Hand [1]. 1909 wurde von Moser die diffuse Entität am Sprunggelenk beschrieben, ohne dass bis dato eine einheitliche Nomenklatur oder Klarheit über das Krankheitsbild existierten [2]. Erst 1941 wurde der Begriff der PVNS durch Jaffe, Lichtenstein und Sutro geprägt [3].
Die Ätiologie der Läsion ist dabei nicht vollends geklärt. So wurden ähnlich wie bei der herkömmlichen Arthritis inflammatorische Reaktionen der Synovialmembran, Traumata [4] oder auch genetische Komponenten, bei gehäuft aufgefundener Expression von kolonie-stimulierendem Faktor 1 (CSF1) und häufiger t(1;2) Translokation, als Ursache diskutiert [5].
Die Inzidenz ist je nach Literatur sehr variabel, insgesamt jedoch eher gering mit durchschnittlich etwa 1,8 - 2 Fällen / 100.000 Einwohnern [6]. Laut einer dänischen Studie aus dem Jahr 2012 beträgt die Inzidenz in Dänemark allerdings sogar 11-44%, je nach Subform [7]. Dies stützt die Vermutung einer höheren Inzidenz bei einer gewissen Dunkelziffer mangels registrierter Fälle.
Das Alter der Erkrankten liegt in der Regel zwischen dem 20. und 40. Lebensjahr mit einem klaren Häufigkeitsgipfel zwischen dem 3. und 4. Lebensjahrzehnt [3]. Die Verteilung auf Mann und Frau ist etwa gleich [8].
Heute unterscheidet man zwei Subformen: die lokale (noduläre) von der diffusen (villösen) Form [9]. Erstere findet sich eher intraartikulär, wobei letztere vor allem extraartikulär zu finden ist. Meist ist nur ein Gelenk betroffen, wobei das Vorkommen aber ubiquitär (kleine- oder große Gelenke und deren Sehnenscheiden) möglich ist. Dabei ist das Kniegelenk am häufigsten (etwa 60%) betroffen; Folgend die Häufigkeit des Befalls in absteigender Reihenfolge: Hüfte, Sprunggelenk, Schulter, Ellbogen, etc. [4].
Das Beschwerdebild der Patienten ist sehr heterogen und reicht von einer schmerzlosen Gelenkschwellung über Schmerzen, Einklemmung oder Fremdkörpergefühl bis hin zur völligen Immobilisierung [10].

Die frühzeitige Diagnostik spielt eine entscheidende Rolle um die seltene Erkrankung zu detektieren und einen meist langjährigen destruktiven Krankheitsverlauf zu verhindern. Konventionelles Röntgen, Magnetresonanztomographie (MRT), Computertomographie (CT) und eine Biopsie zur histologischen Aufarbeitung stellen dabei die gängigsten Verfahren dar.

Versuche mit hämatologischen, biochemischen und immunologischen Untersuchungen allein blieben erfolglos [11].
Während man im Röntgenbild, in etwa 33% der diffusen und 25% der lokalen Fälle nur in späteren Stadien erosive, zystische und partiell sklerosierende Knochenläsionen findet, stellt das MRT die sensitivste der nicht invasiven Methoden mit typischen Signalauslöschungen durch Eisenpigmente dar [12], [13]. Histologisch findet man im Tenosynovialgewebe eine Proliferation von Synoviozyten, was nachfolgend eine Einwanderung von Entzündungszellen wie z.B. Histiozyten und mit Hämosiderin beladenen Makrophagen zur Folge hat [14].
Intraoperativ, beispielsweise mittels einer Arthroskopie des Kniegelenks oder bei offenem Zugang, zeigen sich typische bräunlich-gelbe, manchmal grünliche Beläge bzw. Schwellungen, die ebenfalls durch eingelagerte Eisenpigmente verursacht werden.
Therapeutisch von großer Wichtigkeit für das Langzeitergebnis, vor allem in Hinblick auf die Rezidivrate, ist die operative Sanierung. Den Goldstandard stellen hierbei die offene Synovektomie bei diffusem Befall bzw. die marginale Exzision in lokalen Formen dar [15]. Dies kann entweder arthroskopisch, offen oder als Kombinationsverfahren geschehen, was kontrovers diskutiert wird [16].

Bei sehr weit fortgeschrittenen Krankheitsverläufen mit ausgeprägten Knorpel-/Knochenschäden oder Zustand nach mehrfachen Rezidiven kommen auch Totalendoprothesen, überwiegend an Knie und Hüfte, oder gar eine Arthrodese, zum Beispiel des Sprunggelenks, in Frage.
Je nach Gründlichkeit und Erfahrung des Chirurgen werden in der Literatur Rezidivraten von 15 bis 56 % beschrieben [10]. Dabei ist die diffuse deutlich aggressiver als die lokale Form, sodass bei inkompletter, nur partieller Synovektomie Rezidivraten bis 50% genannt werden [16]. Gelingt eine vollständige Resektion ist das Lokalrezidiv mit etwa 10 % deutlich geringer.
Um die Rezidivrate postoperativ zu senken oder vorhandene Rezidive zu behandeln stehen im Rahmen der adjuvanten Therapie die perkutane Strahlentherapie [17], die Radiosynoviorthese (RSO) [18] mit Yttrium-90 [19] und neuerdings eine Antikörpertherapie zur Verfügung [20].
Hierbei gilt es aber die Indikation streng zu stellen, auf die individuelle Situation des Patienten zu achten und die verfahrensspezifischen Nebenwirkungen zu bedenken. So eignet sich die herkömmliche perkutane Strahlentherapie vor Allem für fulminante Krankheitsverläufe, in denen eine chirurgische Sanierung nicht möglich ist oder bei schlecht resektablen lokalen Rezidiven [20]. Als Nachteil ist zweifelsohne das Risiko einer Zweitneoplasie durch ionisierende Strahlung zu nennen. Die RSO, bei der ein Beta-Strahler in das betroffene Gelenk injiziert wird, kann nur an Gelenken mit Gelenkkapsel als präformiertem Hohlraum angewendet werden und nicht entlang von Sehnen.

Pexidartinib (PLX3397), ein selektiver CSF1R-Inhibitor, ist aktuell in Studien mit kleiner Fallzahl als erfolgsversprechend beschrieben worden, was jedoch weiteren Langzeitstudien bedürfe [21]. Zudem wäre eine Dauertherapie notwendig. Auch ist das Spektrum an unerwünschten Nebenwirkungen durchaus relevant.
Imatinib als weiterer Vertreter der Tyrosinkinase-Inhibitoren, der via Blockade des überexprimierten CSF1-Rezeptors wirkt, werden krankheitsstabilisiernde Effekte zugeschrieben [22].
Eine weitere Option ist der vaskuläre-endotheliale-Wachstumsfaktor-Antikörper (VEGF-antibody) Bevacizumab, der an bestimmten Gefäßwandanteilen ansetzt [23].

4. Zielsetzung der Untersuchungen

Unsere Zielsetzung der beiden Arbeiten war einerseits, an einem Zentrum mit entsprechender Fallzahl an betroffenen Patienten, eine retrospektive Übersichtsarbeit mit den generellen Charakteristika der PVNS und Spezifika von Behandlung und Ergebnissen zu erstellen. Dabei fokussiert sich die erste Arbeit auf die ausgedehnte, aggressive chirurgische Sanierung.
In einem zweiten Schritt haben wir das am häufigsten betroffene Kniegelenk herausgesucht und die adjuvante Therapieform der RSO bezüglich Einfluss auf das Lokalrezidiv (LR) genauer untersucht.

5. Übersicht

5.1 Methoden

In die Datenbank wurden 122 Operationen an 105 Patienten im Alter von 12 - 82 Jahren, die von 1996 bis 2014 an unserer Institution durchgeführt wurden, aufgenommen. Dabei wurden alle Läsionen mit Verdacht auf PVNS histopathologisch bestätigt und mittels MRT präoperativ die Lage und das Ausmaß der Erkrankung bestimmt.
Alle Patienten erhielten eine offene Synovektomie, die in manchen Fällen durch eine diagnostische Arthroskopie ergänzt wurde. Für das Kniegelenk wurde eine Kombination aus ventraler und dorsaler Synovektomie für den diffusen Subtyp oder eine “mini-open” Resektion bei lokalen Formen angewandt. Bei sehr stark ausgeprägtem Verlauf erfolgte eine zweizeitige Resektion (ventral gefolgt von dorsal). Nachfolgend erhielten 2 Patienten eine adjuvante Bestrahlung und 27 eine RSO.
Bei den 32 Patienten, deren Knie mit dem diffusen Typ befallen war, erfolgten insgesamt 37 chirurgische Interventionen. Anschließend erhielten davon 26 Patienten eine Dreiphasen-Knochenszintigraphie sowie RSO und 11 keine (Kontrollgruppe).

Das Follow-up wurde nach festgelegten zeitlichen Intervallen mittels MRT durchgeführt. Die statistische Auswertung erfolgte mittels üblicher Methoden nach Kaplan-Meier, Log-Rank Test und Chi-Quadrat Test. Die Durchführung der Studien erfolgte nach Genehmigung durch die Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München (P 17-889) und mit schriftlichem Einverständnis der Patienten.

5.2 Ergebnisse

Bei einer medianen Nachsorge von 71 Monaten (13-238), wobei zwei Patienten währenddessen ausschieden aufgrund von fehlender Erreichbarkeit, zeigte sich in 22 (18%) Fällen ein Rezidiv innerhalb von durchschnittlich 18 Monaten, wobei >90% der Rezidive in den ersten drei Jahren auftraten. Hierbei waren von den 22 Rezidiven 9 (11%) Primär-Rezidive und 13 (34%) Sekundär-Rezidive.
Am Ende unserer Nachuntersuchung (nach Resektion auch von Rezidivbefunden) zeigten sich 6 (5%) von 120 Resektionen mit einer Persistenz des Tumors. Auf die Patientenzahl bezogen (n = 103) sind das 5.8%.
In 66 (54%) Fällen fand sich histopathologisch der diffuse Typ.
Bezüglich der Patienten, die bei diffusem Typ des Knies operiert wurden, kam es im Mittel nach 19 Monaten postoperativ in 9 (24%) Fällen zum Rezidiv. Von diesen 9 Rezidiven waren 3 (17%) Erst-Rezidive und 6 (32%) Re-Rezidive. In 26 Fällen wurde eine RSO durchgeführt, wovon 6 (23%) ein Rezidiv entwickelten. In der Kontrollgruppe ohne RSO zeigten 3 von 11 (27%) Patienten ein Rezidiv [24], [25].

5.3 Schlussfolgerungen

Das Krankheitsbild der Pigmentierten villonodulären Synovialitis ist eine sehr seltene, gutartige Neoplasie ausgehend von der Synovialmembran mit Ausbreitung in den Gelenken und entlang von Sehnenscheiden. Dies führt mitunter zu einem hohen Leidensdruck der Patienten und bringt zum Teil grosse Einschränkungen in der Mobilität im Alltag mit sich.
Wie in beiden Studien gezeigt gibt es gute Möglichkeiten kurativ einzugreifen. Dabei stellt die aggressive chirurgische Intervention den Goldstandard dar, welche allerdings mitunter schwierig durchzuführen ist und hohe operative Erfahrung erfordert.
In der Nachbehandlung stehen diverse Optionen zur Verfügung, wobei wir erstmals in der Literatur eine vergleichende Untersuchung zur RSO an einem homogenen Krankengut durchführen konnten. Die RSO ermöglicht dabei auch Patienten mit hohem Risiko eines Lokalrezidivs auf das geringere Risiko einer Vergleichsgruppe zurückzuführen. Als alleinige Alternative zur aggressiven operativen Resektion oder adjuvanten Kompensation bei mangelhafter Entfernung kann sie somit nicht gelten.

Für die Gesamtpopulation gilt es eine weitreichende Aufklärung über das Krankheitsbild bei Ärzten, medizinisch tätigen Personal und Patienten voranzubringen um eine frühzeitig adäquate Diagnostik und Therapie zu erreichen.
Projekte wie die Etablierung von Patientenselbsthilfegruppen dienen zum Austausch von persönlichen Erfahrungen und aktuellen Möglichkeiten der Therapie und verbessern den Umgang im Alltag mit dieser Krankheit.

6. Overview

6.1. Methods

122 surgeries on 105 patients aged 12 - 82 years, performed at our institution from 1996 to 2014, were included in the database. All lesions with suspected PVNS were confirmed histopathologically and the location and extent were defined preoperative by MRI.
All patients received an open synovectomy, in some cases supplemented by arthroscopy. For the knee joint a combination of anterior and posterior synovectomy for the diffuse subtype or "mini-open" resections in local forms were applied. If the disease was extended, a two-stage resection was performed. Subsequently, 2 patients received adjuvant radiation and 27 patients a RSO.
In the 32 patients whose knees were affected by the diffuse type, a total of 37 surgical interventions were performed. Subsequently, 26 patients received RSO,11 none.
The follow-up was performed by MRI at fixed intervals. Statistical evaluation was performed using standard methods such as Kaplan-Meier, Log-Rank Test and Chi-Square Test.
The studies were conducted after approval by the Ethics Commission of the Medical Faculty of the Ludwig-Maximilians-University Munich (P 17-889) and after obtaining written consent of the patients.

6.2. Results

The median follow-up time was 71 months (13-238). Two patients were lost to follow up as a result of poor access. 22 (18%) cases had a recurrence within 18 months and >90% of total recurrences occurred within the first three years.
Of the 22 resections who had recurrence within 18 months, 9 (11%) and 13 (34%) had primary and secondary recurrences respectively.
After additional resections, and at the end of the follow up period, 6 individuals had a persistence of their malignancy. This constituted 5.8% of patients (n=103) and 5% of total resections performed (n=120).
Diffuse histopathology of the knee was found in 66 cases (54%).

Of the patients with diffuse pathology who were operated on, 9 (24%) resections had recurrence of after 19 months. Of these 9 cases, 3 (17%) had a primary recurrence and 6 (32%) secondary. 26 lesions were treated with RSO and 6 (23%) developed a recurrence. In the control group, who did not undergone RSO, 3 (27%) patients had a recurrence (n=11) [24], [25].

6.3. Conclusions

The picture of pigmented villonodular synovitis is a rare, benign proliferation starting from the synovial membrane with spread in the joints and along tendon sheaths. This sometimes leads to a high degree of suffering and results in major restrictions in mobility in everyday life.
As shown in our two studies, however, there are good possibilities for curative intervention. Aggressive surgical interventions represent the gold standard. There are various options available for follow-up treatment.
We have not been able to demonstrate a positive effect of adjuvant radiosynoviorthesis (RSO), at the knee joint. We think RSO is effective in reducing the high number of local recurrences in high risk patients which brings the risk in those patients down to the lower risk of the control group. But it cannot be regarded as the an alternative to aggressive surgical resection or adjuvant compensation for inadequate resection.
Teaching the typical clinical and radiological picture of PVS must be promoted so that it can be recognised and treated at an early stage.

Projects such establishment of patients groups to exchange experiences and therapies may improve the way the patients deal with this disease in their everyday lives.

7. Eigenanteil an den vorgelegten Arbeiten

Der Beitrag des Doktoranden Carl Ferdinand Capellen, der in dem Fachartikel “Lowering the recurrence rate in pigmented villonodular synovitis: A series of 120 resections” als Erstautor und in “The effects of radiosynoviorthesis in pigmented villonodular synovitis of the knee” als Ko-Autor auftritt, umfasst zum einen die Kontaktaufnahme mit den Patienten, sowie die eigenständige Erhebung und Auswertung der Patientendaten. Zum anderen war er in Zusammenarbeit mit Prof. Dr. H.R. Dürr an der klinischen Interpretation der Daten, Literaturrecherche sowie an der Verfassung und Überarbeitung beider Veröffentlichungen maßgeblich beteiligt.

8. Veröffentlichung I

RHEUMATOLOGY

Concise report

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Lowering the recurrence rate in pigmented villonodular synovitis: A series of 120 resections

Carl Ferdinand Capellen[1], Reinhold Tiling[2], Alexander Klein[1], Andrea Baur-Melnyk[3], Thomas Knösel[4], Christof Birkenmaier[1], Falk Roeder[5,6], Volkmar Jansson[1] and Hans Roland Dürr[1]

Abstract

Objectives. Tenosynovial giant-cell tumour or pigmented villonodular synovitis is an aggressive synovial proliferative disease, with the knee joint being the most commonly affected joint. The mainstay of therapy is surgical resection. The aim of this study was to evaluate the main patient characteristics, treatment and outcomes in a large single-centre retrospective study, focusing on meticulous aggressive open surgical procedures.

Methods. From 1996 through 2014, 122 surgical interventions were performed in 105 patients. All patients underwent open synovectomy and when the knee joint was affected, combined anterior and posterior synovectomy. Radiotherapy was applied in 2 patients, radiosynoviorthesis in 27 patients.

Results. In histopathology, the diffuse type was seen in 66 (54%) lesions. Two patients were lost during follow-up. At a median follow-up time of 71 months (range: 13–238), 22 (18%) lesions recurred within a median of 18 months, >90% in the first 3 years. Out of those 22 recurrences, 9 (11%) were seen in primary disease and 13 (34%) were a second recurrence. After renewed resection, 6 (5%) out of the 120 resections had persistent tumour at the end of follow-up. Based on the number of patients with complete follow-up ($n = 103$), this represents 5.8%.

Conclusion. In diffuse-type pigmented villonodular synovitis, total synovectomy might be difficult to achieve. As shown in our results and also in the literature, meticulous open resection, especially in difficult to approach areas such as the popliteal space, reduces local recurrence rates. External beam radiation is an option in prevention of otherwise non-operable local recurrences or in non-operable disease.

Key words: tenosynovial giant-cell tumour, PVS, surgery, recurrence, prognostic factors

CLINICAL SCIENCE

Rheumatology key messages

- Pigmented villonodular synovitis has a high risk of recurrence after synovectomy in the first 3 years.
- Patients with already recurring lesions of pigmented villonodular synovitis are especially at risk for further recurrence.
- Meticulous surgical resection reduces local recurrence rate in pigmented villonodular synovitis to less than 10%.

Introduction

Tenosynovial giant-cell tumour, historically known as pigmented villonodular synovitis (PVS), is a benign but aggressive synovial proliferative lesion. It was first described by Chassaignac [1] and termed PVS by Jaffe *et al.* [2]. PVS is rare with an annual incidence of about 1.8 patients/million and with a peak in the third or fourth decade of life [3]. The knee joint is the most commonly affected, followed by the hip and ankle joints [4]. In tenosynovial tissue, a proliferation of synoviocytes attracts inflammatory cells such as histiocytes and hemosiderin-laden macrophages [5]. We now distinguish the localized (nodular)—where brownish, villous and nodular tissue is seen, sometimes invading the adjacent bone—from the diffuse type [6].

The aetiology of the lesion is still unknown but neoplastic clones found in PVS often express colony-stimulating factor 1 (CSF1) and frequently have a t(1; 2) translocation [7]. Malignant transformation is reported in very few cases [8]. Clinical presentation is nonspecific with symptoms

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such as swelling, pain and joint locking caused by nodular lesions [9].

The mainstay of therapy is surgical resection either with marginal excision in localized disease or with total synovectomy in diffusely involved joints or tendon sheaths. There is still controversy whether this should be done by aggressive open synovectomy or by an arthroscopic approach, if feasible [10, 11]. Conventional radiotherapy as well as radiosynoviorthesis might also affect the rate of local recurrence (LR) or even cure the disease [12]. In recent years, systemic antibody treatment with PLX3397, a selective CSF1 receptor inhibitor, has shown some favourable results [5].

The aim of our study was to evaluate the main patient characteristics, treatment and outcomes in a large single-centre retrospective study, focusing on meticulous aggressive open surgical procedures.

Methods

Patient characteristics

From 1996 through 2014, 105 consecutive patients with PVS were treated at our institution and a total of 122 surgical interventions were performed. All lesions had a diagnosis of PVS based on histological features and immunohistochemistry. In most cases, MRI was used to preoperatively define the size and localization of the tumour.

The median age of the 58 male and 47 female patients was 42 years (range: 12–82) showing two peaks at 20–30 and 40–50 years, respectively. The affected anatomical region was the knee joint in 58 patients, the feet in 16, the hand in 11, the ankle joint in 9, the hip joint in 4, the elbow joint and soft tissue at the lower calf with 2 each, and sacral joints, soft tissue of the upper calf and shoulder with 1 each. Pain (54%), swelling (40%), joint effusion (12%) and knee locking (3%) were the typical symptoms. The median duration of symptoms until diagnosis was 8 months (range: 0–428). For detection of recurrent lesions, sequential MRI had been used. Forty of the 122 resected lesions were already recurrences after previous surgical resections.

Treatment characteristics

All patients underwent open synovectomy and in some cases, an additional arthroscopy was performed for diagnostic reasons. At the knee, a combined anterior and posterior synovectomy in diffuse PVS or mini open resections in nodular diseases were performed. In large lesions (e.g. involvement of all parts of the hind and middle foot), a two-stage resection was performed. Adjuvant radiotherapy was applied in 2 patients and radiosynoviorthesis in 27 cases at the knee following a standardized protocol 6–8 weeks after surgery: under sterile conditions, 185 MBq (5 mCi) of 90Y-colloid was administered, after the intraarticular position of the needle tip was ensured by an injection of radiopaque contrast under fluoroscopy.

Follow-up evaluation and statistical analysis

All but two patients could be contacted for this study. No patient had deceased. MRI was the standard imaging modality for follow-up, starting 3 months after surgery, followed by every 3 months in the first year, every 6 months in the second year and then yearly for 5 years. However, not all patients adhered strictly to that schedule. Recurrence was defined either as a progressive lesion with the typical appearance of PVS in MRI or by conclusive histopathology from repeat excisions. The time to recurrence was calculated from the date of surgery to the date of the first imaging study with a recurrence (as diagnosed by imaging directly or by later histopathology).

The study was approved by the Ethics Committee of the Faculty of Medicine, Ludwig-Maximilians-University Munich (P 17-889). Written consent was obtained from all patients.

For statistical analysis, the recurrence-free survival was calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank test or the Chi-square test. The data analysis software used was MedCalc, MedCalc Software, Ostend, Belgium.

Results

Diffuse PVS was seen in 66 (54%) lesions. Two patients could not be contacted, leaving 120 resections in 103 patients for follow-up. At a median follow-up time of 71 months post-surgery (range: 13–238), 98 of the 120 resected patients showed no evidence of LR. Twenty-two lesions recurred within a median of 18 months (range: 3–75) after surgery (Fig. 1). Of those 22 recurrences, 9 (11%) were seen in primary disease whereas 13 (34%) were in already recurring cases (Fig. 2). Our LR rate was 18% in total.

Including all locations, there was no statistically significant difference between LR in diffuse and nodular forms with regards to recurrence. At the knee, 8 of 36 (22%) diffuse and 3 of 28 (11%) nodular lesions recurred (not significant). Out of 29 patients who came to our department with LR after having had the index surgery at other institutions, 10 recurred again. Seven out of those 10 patients had further surgery with one LR treated in a third surgery, which then again led to LR. Out of nine patients with LR after initial resection at our institution, seven had additional surgery, one recurred again and is disease-free after a third surgery. In total, 6 out of 120 resection patients (5%) had persistent tumour at the latest follow-up. Based on the number of patients with complete follow-up ($n = 103$) this represents 5.8%.

Regarding radiotherapy, none of the two patients showed recurrent disease. In 27 patients with adjuvant radiosynoviorthesis, 7 (32%) recurred.

Six surgical complications were encountered in total: one necrosis of the femoral condyle after total synovectomy of the knee and repeated radiosynoviorthesis/radiosynovectomy; one peroneal nerve palsy with total recovery; one deep infection; one instability of the collateral ligament at the knee; and two wound revisions due to haematomas.

Fig. 1 Local recurrence-free survival in 120 surgical resections of PVS

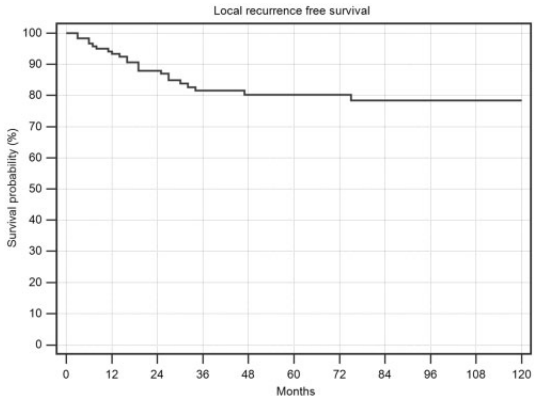
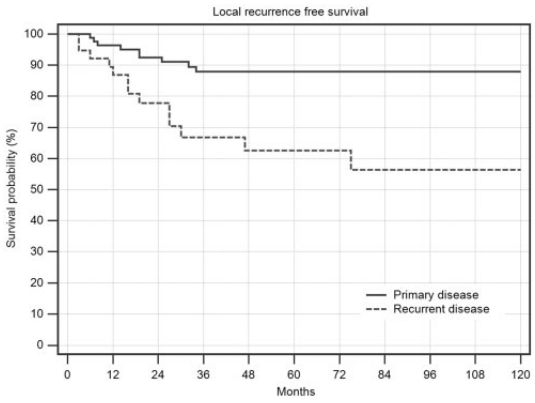


Fig. 2 The impact of recurrent disease on local recurrence-free survival ($P = 0.0009$)



PVS: pigmented villonodular synovitis.

Discussion

As described in literature, PVS shows a predilection for young adults. In our large series, we found a previously undescribed double-peak distribution, with the first peak between 20 and 30 and the second between 40 and 50 years of age. Beyond these two peaks, we also saw very young or much older patients with PVS. The latter group had in some cases PVS diagnosed by coincidence in the context of an arthroplasty procedure and in consequence received additional synovectomy. There was no statistically significant sex difference in our series, but we observed a tendency towards males, which is in contrast to most previsously published studies [13]. The duration of symptoms prior to diagnosis was also independent of sex. Our study does not focus on the diagnosis of PVS. MRI is a well-established standard and was used for primary diagnosis and in follow-up [14, 15].

Surgery remains the mainstay of therapy, but there is no generally accepted standard as to what type of surgical procedure should be preferred. Primarily with knee joint PVS, but also when the hip is affected, arthroscopic and open synovectomy are competing treatment modalities. In a survey including 173 patients from 10 centres in Germany and Austria, the rate of LR was very much dependent on the number of cases treated [9]. Institutions with $<$20 cases per year had an LR of 56%, those with greater numbers ranged between 15 and 37%. In a large meta-analysis including 630 patients with PVS of the knee, in diffuse disease with open synovectomy or the combination of open and arthroscopic synovectomy and adjuvant external beam radiotherapy or radiosynoviorthesis in open and combined surgery, lower rates of LR (24 and 14%) as compared with arthroscopic synovectomy (38%) could be shown. In the localized lesions, there was no difference between the subgroups (LR 6–8%) [10]. This reflects our own experience with a LR at the knee of 22% in diffuse and 11% in localized forms, and either open or combined open and arthroscopic procedures. It is worth mentioning that the rate of joint stiffness was higher (11%) after open surgery as compared with arthroscopic (2%). A careful physical rehabilitation program therefore seems important especially after open synovectomies. These results are in contrast to another large meta-analysis on the same subject including 1019 patients [16]. In localized disease, LR was 7–9% for both methods whereas in the diffuse form, arthroscopic surgery did better (16%) than open surgery (23%). Complications are described in 0% of arthroscopic resections and 19% of open synovectomy. However, in that study radiotherapy in either form was not a selection criterion.

The largest analysis with 214 PVS cases at the knee was performed in the UK [11] with the chosen treatment being nearly exclusively open synovectomy. In this series, LR was 48% in diffuse forms and 9% in localized disease. The authors did not discuss this specifically, but these surprisingly poor results in diffuse forms might be due to the fact that six different surgeons had performed those cases over several years. The number of recurrent cases at presentation (12%) in the UK study offers no adequate explanation for those results (this study 29/105, 28%). So as clearly shown by Bruns *et al.* [9], experience and meticulous surgery is most important in aggressive diffuse lesions.

During follow-up, one-third of LR were within the first year, another third in the second and $<$10% after 3 years. Therefore, follow-up MRIs every 6 months during the first 3 years should be able to detect $>$90% of all LR. LR has a good chance of cure by additional surgery. LR in recurring lesions was in total 34%, but eventually, 94% of the patients were free of tumour.

Radiotherapy is a valid option in patients with diffuse disease that cannot be treated by means of surgery. Park *et al.* [12] reported LR rates in 4 of 23 patients (17%) treated with 12–34 Gy of external beam radiation with PVS of the knee. But in all of these patients, either arthroscopic or open synovectomy was performed prior to radiation. An LR of 0% after arthroscopic resection and

radiotherapy with 20–30 Gy in 26 patients was reported by Li *et al.* [17]. Adjuvant radiosynoviorthesis/radiosynovectomy with Yttrium-90 is also used in many patients especially at the knee, and this was also the case in our study. There are reports of favourable outcomes but there is no clear indication for this method of treatment [18, 19].

New approaches with an antibody-mediated inhibition of the CSF1 receptor-kinase in a dose escalation study on 41 patients showed stable disease in eight cases and one partial response. The subsequent treatment study in 23 patients showed 12 patients with stable disease and 7 with a partial response [5].

Conclusions

PVS is a rare aggressive lesion affecting most often the knee but also any other synovial tissue. In localized disease, marginal resection shows favourable results whereas in diffuse forms, total synovectomy might be difficult to achieve. As shown in our own results as well as in the literature, meticulous resection especially in difficult to approach areas like the popliteal space reduces LR rates. Adjuvant external beam radiation is an option in prevention of otherwise non-operable LRs or in non-operable disease. In follow-up, two-thirds of LR were diagnosed during the first 2 years, and $<10\%$ after 3 years. A follow-up MRI every 6 months during the first 3 years should be able to detect $>90\%$ of all LR.

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Each author has contributed significantly to, and is willing to take public responsibility for, this study: its design, data acquisition and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. C.F.C.: student doing his thesis on PVS, contacted the patients and collected the data, involved in drafting and revising of the manuscript. R.T.: nuclear medicine, did the radiosynoviorthesis, involved in drafting and revising of the manuscript. A.K.: surgeon, involved in drafting and revising of the manuscript. A.B.-M.: radiologist, involved in drafting and revising of the manuscript. T.K.: pathologist, involved in drafting and revising of the manuscript. F.R.: reviewing the radiotherapy and deciding which patient to treat or not to treat, involved in drafting and revising of the manuscript. C.B.: surgeon, involved in drafting and revising of the manuscript. V.J.: surgeon, involved in drafting and revising of the manuscript. H.R.D.: corresponding author, developed the study concept, did the final data analysis and provided the major clinical input in writing and revising of the manuscript. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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9. Veröffentlichung II

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ORTHOPAEDIC SURGERY

The effects of radiosynoviorthesis in pigmented villonodular synovitis of the knee

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Abstract

Introduction Tenosynovial giant-cell tumor also known as pigmented villonodular synovitis (PVS) is a benign but aggressive synovial proliferative disease most often affecting the knee joint. The mainstay of therapy is surgical resection. Due to a high rate of local recurrence, radiosynoviorthesis (RSO) is used as an adjuvant method in many cases. The aim of this study was to compare local recurrence (LR) rates after surgical synovectomy with and without adjuvant RSO.

Materials and methods From 1996 to 2014, 37 surgical interventions were performed in 32 patients with diffuse pigmented villonodular synovitis of the knee. All patients underwent open synovectomy. Adjuvant radiosynoviorthesis (RSO) was applied in 26 cases, the control group consists of 11 cases without RSO.

Results 9 (24%) lesions recurred within a median of 19 months after surgery. Of those 9 recurrences, 3 (17%) were seen in primary disease, 6 (32%) in already recurring cases (n.s.). In 26 RSO treated patients 6 (23%) recurred, in 11 patients of the control group, 3 (27%) recurred (n.s.).

Conclusions RSO is effective in PVS as also shown in some smaller reports in the literature. But surgery is still the mainstay of therapy. RSO is not a method of compensating for an insufficient surgical approach, but it may reduce the high rate of LR in patients with large and even recurrent diffuse forms of the disease.

Keywords Synovitis · Pigmented villonodular · Giant cell tumor of tendon sheath · Synovectomy · Neoplasm recurrence · Local · Radiosynoviorthesis

Introduction

Tenosynovial giant-cell tumor, historically known as pigmented villonodular synovitis (PVS) is a benign but aggressive synovial proliferative condition [4, 10]. PVS is comparatively rare with an annual incidence of about 1.8 patients/million and occurs especially in adults in their third or fourth decade of life [16]. The knee joint is the most commonly affected joint in about 50% [24].

The etiology of the lesion is unknown, but neoplastic clones found in PVS often express colony-stimulating factor 1 (CSF1) and frequently have a $t(1; 2)$ translocation [23]. In the localized (nodular) as well as in the diffuse form, brownish, villous and nodular growth can be observed, sometimes invading the adjacent bone [14]. The clinical presentation is nonspecific with symptoms such as swelling, pain and joints locking caused by interposition of nodular lesions [2].

The mainstay of therapy is surgical resection either with marginal excision in localized disease or with total synovectomy in diffusely involved joints or tendon sheaths [6]. Conventional radiotherapy, as well as radiosynoviorthesis might also affect the rate of local recurrence or even cure the disease [19]. Local recurrence (LR) is seen in more than 20% of the cases localized in the knee with the diffuse form of the disease [1]. Therefore, adjuvant intra-articular radiation synovectomy—radiosynoviorthesis—(RSO) has been employed for decades to reduce the risk of LR. The published results in some very small series of patients seem

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to be favorable (Table 1) but due to a lack of comparative studies with and without RSO, the overall benefits of RSO still remain unclear.

The aim of our study was to evaluate the treatment outcomes in a large single-centre retrospective study comparing patients after surgical synovectomy with and without adjuvant RSO.

Patients and methods

Patients

Between 1996 and 2014, 105 consecutive patients with PVS were treated in our institution and a total of 122 surgical interventions were performed. All lesions had a diagnosis of PVS based on histological features and immunohistochemistry. Preoperatively, predominantly magnetic resonance imaging (MRI) was used to define the size and localization of the tumor. All patients underwent surgical resections. This group has been described in detail before [3]. Out of those 58 (55%) patients had an involvement of the knee of which 26 (45%) were of the nodular type and 32 (55%) showed diffuse disease.

These latter 32 patients together with 37 surgeries constitute the study population. RSO was performed in 26 cases (70%). 11 Cases without RSO were used as the control.

The mean age in both groups was 49 (14–82) years. The RSO group consisted of 12 male and 14 female patients and the control group of 4 male and 7 female patients (n.s.). Patients with already recurrent disease were seen in 50% (RSO) and 46% (control) (n.s.).

The mean duration of symptoms prior to diagnosis was 26 (0–151) months in the RSO and 19.4 (0–115) months in the control group (n.s.). Progressive MRI findings were used as a marker of LR.

All patients underwent open synovectomy, in some cases additional arthroscopy for diagnostic reasons was performed prior to the actual surgical resection which consisted of a combined anterior and posterior open synovectomy. Adjuvant external beam radiotherapy or systemic targeted therapy were not utilized.

Three-phase bone scintigraphy

Three-phase bone scintigraphy was performed 24 h before RSO using a dual-detector (E.CAM, Siemens Medical Solutions, Erlangen, Germany) with a low-energy, high-resolution collimator (LEHR) and the energy window centered on the 140-keV ^{99m}Tc photopeak. Blood flow scans (first phase) consisted of serial dynamic images of the knee acquired for 2 min directly after iv injection of 500 MBq ^{99m}Tc-methylene diphosphonate (^{99m}Tc- MPD). Subsequently, blood pool images (second phase) were obtained for 2 min in the same position. Three hours later, whole-body delayed images (third phase) were acquired using a 15 cm/min table speed.

Radiosynoviorthesis (RSO)

RSO was performed under sterile conditions following a standardized protocol owing to the guidelines after the exclusion of contraindications 6–8 weeks after surgery. Under sterile conditions, the lateral suprapatellar recess was punctured, and 185 MBq (5 mCi) of ^{90}Y-colloid was administered, after the intraarticular position of the needle tip was ensured by an injection of radiopaque contrast under fluoroscopy. Intra-articular distribution of the radiopharmacon was verified by Bremsstrahlung imaging.

Table 1 Systematic review of studies reporting effectiveness of radiosynoviorthesis in PVS

Author	Year	Patients (*n*)	Knee + RSO (*n*)	Recurrent cases* (*n*)	Clinical benefit knee (*n*)	Radiological benefit knee (*n*)
Franssen et al. [7]	1989	8	8	6	4 (50%)	–
Gumpel et al. [8]	1991	9	9	5	6 (67%)	–
Kat et al. [11]	2000	11	8	3	8 (100%)	8 (100%)
Chin et al. [5]	2002	40	30	30	Benefit in score	25 (83%)
Shabat et al. [20]	2002	10	6	4	6 (100%)	6 (100%)
Ward et al. [22]	2007	9	6	0	6 (100%)	5 (83%)
Öztürk et al. [18]	2008	7	7	0	–	7 (100%)
Zook et al. [25]	2011	9	8	7	6 (75%)	–
Ottaviani et al. [17]	2011	122	50	0	Benefit in score	35 (70%)
Koca et al. [12]	2013	15	15	10	13 (87%)	15 (100%)

*Recurrence before treatment in the study

Follow-up

All patients were contacted for this study and no patient had died or been lost to follow-up. MRI was used for follow-up imaging, routinely starting 3 months after surgery, then every 3 months in the 1 year, every 6 months in the second year and then yearly for 5 years. Not all patients adhered strictly to that schedule. Recurrence was defined either as a progressive typical appearance of PVS in MRI or histologically proven in a second surgery. For calculating the time to recurrence, the date of surgery was used as baseline.

Statistical analysis

For statistical analysis, the recurrence-free interval was calculated by the Kaplan–Meier method. Significance analysis was performed using the log-rank test or the Chi-square test. The data analysis software used was MedCalc®.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all the patients included in this study.

Results

At a median follow-up time of 49 months (14–193), 28 of the 37 resected patients showed no evidence of LR. 9 (24%) lesions recurred within a median of 19 months (3–75) after surgery (Fig. 1). From those 9 recurrences, 3 (17%) were seen in primary disease, 6 (32%) in already recurring cases (Fig. 2) (n.s.).

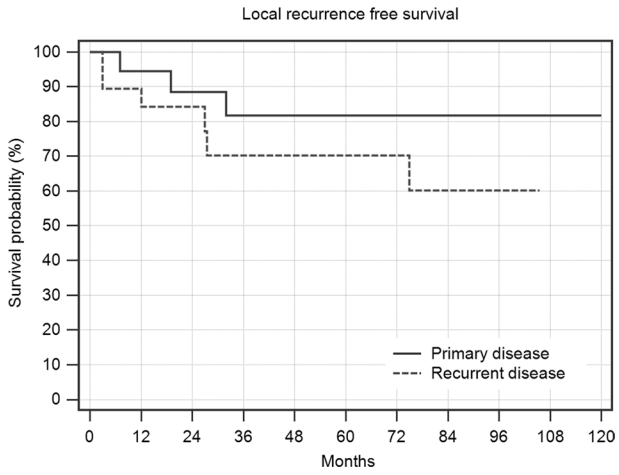

Fig. 2 The impact of recurrent disease on local recurrence-free survival (n.s.)

In 26 RSO treated patients, 6 (23%) recurred, in 11 patients of the control group 3 (27%) recurred (Fig. 3) (n-s.).

In 13 patients with local recurrences after treatment in other hospitals, 5 recurred again following second surgery in our Department. Of those five patients 3 had further surgery with a third LR in one case. In 3 cases with LR after initial resection in our Department, all 3 had a second resection and are disease free at final follow-up. Overall, out of 37 resections, four patients (11%) had LR at final follow-up. All 4 had undergone RSO.

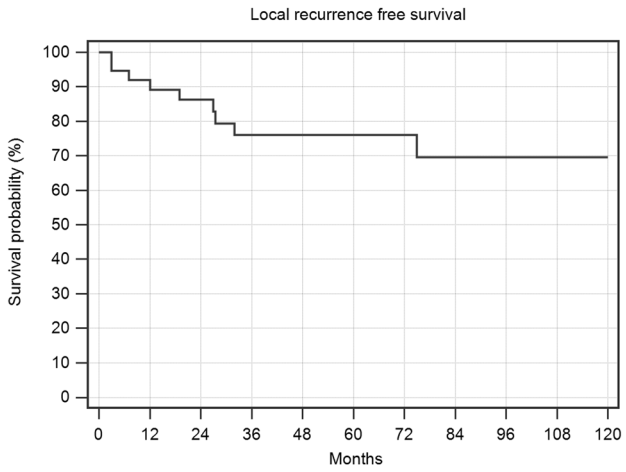

Fig. 1 Local recurrence-free survival in 37 patients with PVS of the knee

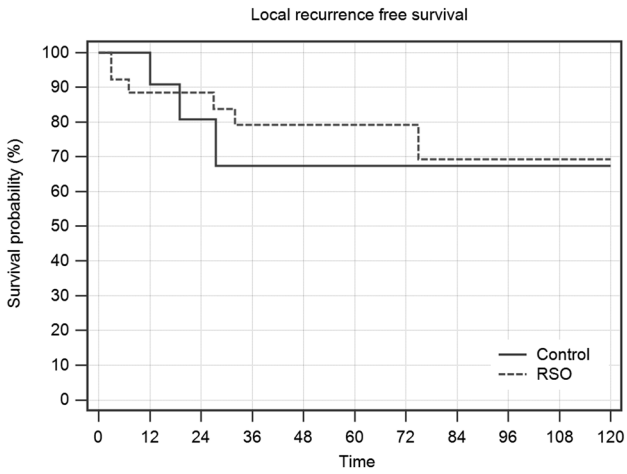

Fig. 3 The impact of Radiosynoviorthesis on local recurrence-free survival (n.s.)

Discussion

Radiosynoviorthesis is effective in diffuse forms of Pigmented Villonodular Synovitis. Even in tight joints as the hip RSO is an option for adjuvant therapy [9]. In this study, RSO reduced the rate of LR in patients with high-risk forms of the disease (large, recurrent, diffuse) to the moderate "normal" risk of diffuse PVS at the knee.

1. Surgery is the mainstay of therapy. In a large meta-analysis including 630 patients with PVS of the knee in diffuse disease with open synovectomy and the combination of open and arthroscopic synovectomy or arthroscopic synovectomy, only LR was seen in 23% and 26%, respectively.
2. To the best of our knowledge, only the study of Chin et al. in 2002 compared 5 patients with surgery alone (LR 0%), 30 with surgery and RSO (LR 15%) and 5 with surgery and external beam radiation (LR 40%). In a subset of studies including RSO, the LR rate was 14% in 43 patients, with external beam radiation 11% in 123 patients, compared to 37% in 282 patients without any form of adjuvant radiation ($p < 0.001$) [15]. The difference was more pronounced in patients receiving arthroscopic synovectomy only. Therefore, the authors concluded that any form of radiation therapy may have most benefit in those patients with residual disease. They also did not see any negative influence of these treatments on joint function or wound healing.

Taking into account only those 3 studies using RSO in more than 10 patients with diffuse PVS at the knee, the rate of LR was 21% in 95 patients. This reflects our own experience. The most optimistic results with 0% LR had been published in small, single-digit case series.

3. The major limitation of our study is its retrospective, non-randomized character. This data has hence to be interpreted with several restrictions. The number of patients with already recurring disease was close to 50%. LR, therefore, had to be expected in a greater number of cases. In primary disease, LR was 17%, leaving not too much opportunity to lower this rate with RSO. In recurrent disease and due to the fact of our institution being a tertiary reference center, many of the cases had extensive disease and hence a worse prognosis from the outset. The indication for RSO might have been as in many retrospective studies biased by the fact that the indication for treatment was especially seen in those patients with an anticipated worse prognosis. However, and notwithstanding these limitations, our data suggests that RSO is not a method of compensating for an insufficient surgical resection, but rather that RSO might reduce the high rate of LR in patients with large and even recurrent diffuse forms of the disease to a risk similar to that of an average patient with a less problematic disease extent.
4. As a second or third step in increasingly aggressive therapy, external beam radiation has to be mentioned as a further option in patients with diffuse disease for which an adequate surgical option does not exist [19]. Park et al. reported LR rates of 4 out of 23 patients (17%) treated with 12–34 Gy of external beam radiation at the knee. But in all of these patients, either arthroscopic or open synovectomy had been performed before. A LR of 0% after arthroscopic resection and radiotherapy with 20–30 Gy in 26 patients was reported by Li et al. [13]. Recently systemic approaches with an antibody blockade of CSF1R Kinase in a dose escalation study in 41 patients showed 8 subjects with stable disease and 1 with a partial response, whereas in the following treatment study on 23 patients, 12 had stable disease and 7 had partial responses [21]. Therefore, this novel therapy might present an additional option for PVS patients who have exhausted local therapies.

Conclusions

Radiosynoviorthesis is effective in diffuse forms of Pigmented Villonodular Synovitis. But surgery is still the mainstay of therapy. RSO is not a method of compensating for an insufficient surgical approach, but it may reduce the high rate of LR in patients with large and even recurrent diffuse forms of the disease. Its use should, therefore, be limited as an adjuvant therapy to patients after total synovectomy leaving no visible disease behind with a considerable risk of local recurrence.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the ethics committee of the Medical Faculty, University of Munich.

Informed consent Written consent was obtained from all patients included in this study.

Data availability The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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