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The effects of radiosynoviorthesis in pigmented villonodular synovitis of the knee

Hans Roland Dürr[1] · Carl Ferdinand Capellen[1] · Alexander Klein[1] · Andrea Baur-Melnyk[3] · Christof Birkenmaier[1] · Volkmar Jansson[1] · Reinhold Tiling[2]

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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

✉ Hans Roland Dürr
hans_roland.duerr@med.uni-muenchen.de

1 Musculoskeletal Oncology, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany

2 Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany

3 Institute of Radiology, University Hospital, LMU Munich, Munich, Germany

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.).

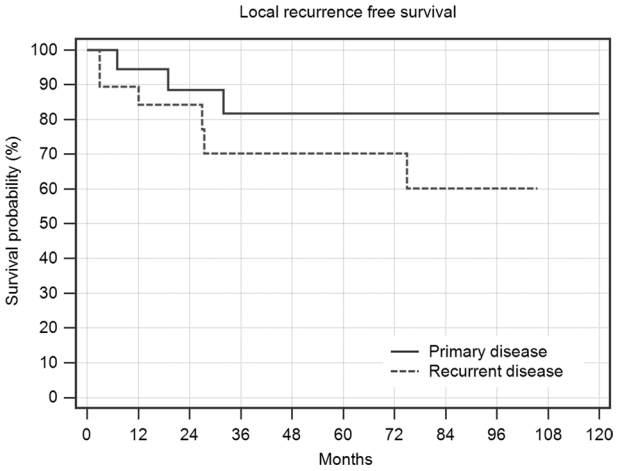

Fig. 2 The impact of recurrent disease on local recurrence-free survival (n.s.)

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.

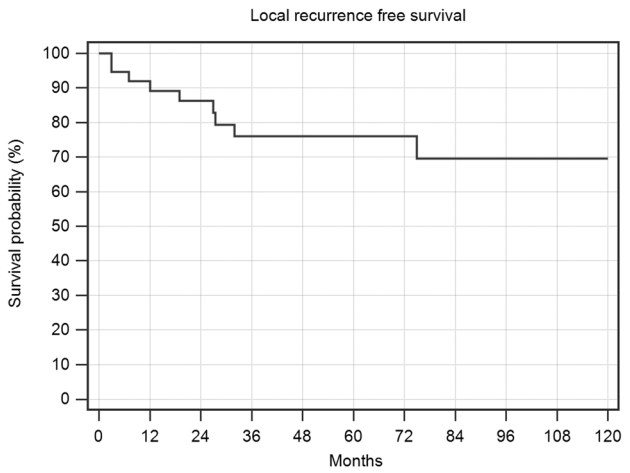

Fig. 1 Local recurrence-free survival in 37 patients with PVS of the knee

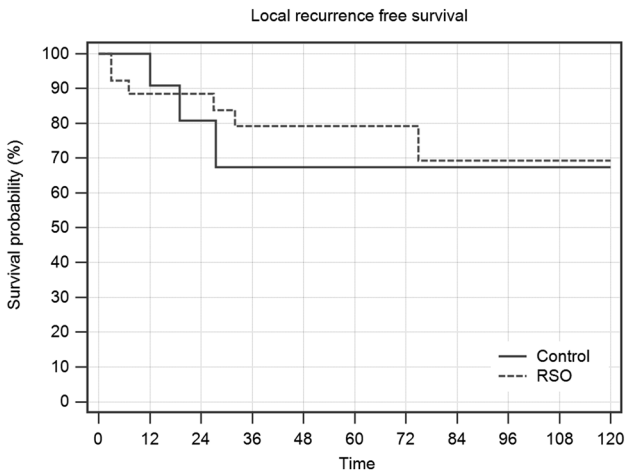

Fig. 3 The impact of Radiosynoviorthesis on local recurrence-free survival (n.s.)

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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