



Management of solitary fibrous tumors localized in extremity: case series and a review of the literature

Ekstremitte yerleşimli soliter fibröz tümörlerin tedavisi:
Olgu serisi ve literatürün gözden geçirilmesi

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ABSTRACT

Objectives: This study aims to evaluate the clinical characteristics and treatment results of patients with a diagnosis of solitary fibrous tumor localized in extremity.

Patients and methods: Clinical findings, treatment methods, clinical outcomes and treatment failures of seven patients (3 males, 4 females; mean age 49.7±20.7 years; range 22 to 79 years) diagnosed as solitary fibrous tumor localized in extremity between January 2005 and December 2016 were evaluated retrospectively.

Results: Most frequent localization was the thigh (42.8%, n=3). Mean tumor size was 10.8±2.4 cm (range 8-15 cm). All patients applied with painless mass and all had primary tumor. All patients had localized disease at the time of diagnosis. Postoperative mean follow-up duration was 44.4 months (range 13-121 months). Marginal resection was performed in two patients at low risk group while wide resection was performed in other patients at moderate and high risk groups. Patients who underwent marginal resection were performed adjuvant radiotherapy. No recurrence or metastasis was detected in any of the patients during follow-up.

Conclusion: In the treatment of solitary fibrous tumors localized in extremity, marginal resection together with radiotherapy may be an alternative treatment method for patients in low risk group according to risk stratification model, for whom wide resection is not possible. Wide resection is recommended in moderate and high risk groups to decrease local recurrence and metastasis risks.

Keywords: Hemangiopericytoma; limb salvage; radiotherapy; solitary fibrous tumor.

ÖZ

Amaç: Bu çalışmada ekstremitte yerleşimli soliter fibröz tümör tanımlı hastaların klinik özellikleri ve tedavi sonuçları değerlendirildi.

Hastalar ve yöntemler: Ocak 2005 - Aralık 2016 tarihleri arasında ekstremitte yerleşimli soliter fibröz tümör tanısı konulan yedi hastanın (3 erkek, 4 kadın; ort. yaş 49,7±20,7 yıl; dağılım 22-79 yıl) klinik bulguları, tedavi yöntemleri, klinik sonuçları ve tedavi başarısızlıkları retrospektif olarak değerlendirildi.

Bulgular: En sık kitle yerleşim yeri uyluk idi (%42,8, n=3). Ortalama tümör boyutu 10,8±2,4 cm (dağılım 8-15 cm) idi. Tüm hastalar ağrısız kitle ile başvurdu ve tümünde primer tümör vardı. Tüm hastalar tanı anında yerleşik hastalığa sahipti. Ameliyat sonrası ortalama takip süresi 44,4 ay (dağılım 13-121 ay) idi. Düşük risk grubunda olan iki hastaya marjinal rezeksiyon, orta ve yüksek risk grubunda olan diğer hastalara geniş eksizeyon uygulandı. Marjinal rezeksiyon geçiren hastalara adjuvan radyoterapi uygulandı. Hiçbir hastada takip sırasında nüks veya metastaz saptanmadı.

Sonuç: Ekstremitte yerleşimli soliter fibröz tümörlerin tedavisinde risk stratifikasyon modeline göre düşük risk grubunda olup geniş rezeksiyonun mümkün olmadığı hastalarda marjinal rezeksiyon ile beraber radyoterapi alternatif bir tedavi yöntemi olabilir. Orta ve yüksek risk grubunda lokal nüks ve metastaz riskinin azaltılması için geniş rezeksiyon önerilmektedir.

Anahtar sözcükler: Hemanjiyoperisitom; uzuv kurtarma; radyoterapi; soliter fibröz tümör.

Solitary fibrous tumors (SFTs) are rare lesions stemmed from primitive fibroblast-like cells in connective tissue.^[1] Despite the fact that SFTs are localized to pleura and other serosal surfaces in general, they may nest in extrapleural soft tissues rarely.^[2]

Extra-pleural SFTs account for 0.6% of all soft tissue tumors.^[3] Soft tissues of extremity are among the rarest site of occurrence; most occur in the proximal lower extremity and tend to have more malignant potential.^[4]

Solitary fibrous tumors principally affect adults between the second and seventh decades of life (median 50 years).^[1] In general, SFTs are benign and good edged tumors. However, there may be 10-15% recurrence or metastases. SFTs in the extremities should be treated with local wide resection in patients without severe disability. If there are evidences that suggest malignant potential, wide resection together with a long-term follow-up and regular magnetic resonance imaging (MRI) controls are advised.^[5]

Adjuvant radiotherapy and chemotherapy are recommended for metastases, recurrence and incomplete resection.^[6] In this study, we aimed to evaluate the clinical characteristics and treatment results of patients with a diagnosis of SFT localized in extremity.

PATIENTS AND METHODS

A total of seven patients (3 males, 4 females; mean age 49.7±20.7 years; range 22 to 79 years) diagnosed as SFT in extremity at Ankara Oncology Training and Research Hospital between January 2005 and December 2016 were evaluated retrospectively. The study protocol was approved by Ankara Oncology Training and Research Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Pathologic material was examined by an experienced soft tissue pathologist and scored for the

presence of a histologically malignant component. According to the risk stratification model they published, Demicco et al.^[7] defined recurrence/metastasis risk in patients as low, medium, and high. Age, tumor size and mitotic figures are reviewed and scores are set as follows:

For age <55: 0 point, ≥55: 1 point; for size (cm) <5 cm: 0 point, 5-10 cm: 1 point, 10-15 cm: 2 points, ≥15 cm: 3 points; for the mitotic figures (/10 high-power fields): 0 mitotic figure: 0 point, 1-3 mitotic figures: 1 point, ≥4 mitotic figures: 2 points. And total scores are set as:

0-2: low malignancy risk, 3-4: moderate malignancy risk, and 5-6: high malignancy risk.

The history, physical examination, posteroanterior lung radiograms, thorax computed tomograms, MRI studies, angiograms and routine laboratory studies of all the patients were analyzed.

All patients were reviewed according to age at diagnosis, primary tumor localization, duration passed before diagnosis, symptoms and findings, size of the tumor, surgical procedure type (marginal excision or wide resection), microscopic surgical margins (inadequate surgical margin was defined as the tumor being 2 mm or closer to the marked margin), chemotherapy, radiotherapy and treatment failures (Table I).

Statistical analysis

All statistical analyses were performed using IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as mean ± standard deviation, frequency and percentage.

RESULTS

All patients applied with primary tumor and had localized disease at the time of diagnosis (Table I). The most frequent localization was anteromedial thigh (42.8%, n=3). There was one patient with

TABLE I

Patient characteristics, reconstruction types and surgical margins

Case	Age/Gender (year)	Localization	Size (cm)	Duration before (months)	Vascular involvement	Nerve infiltration	Resection type	Microscopic surgical margin
1	79/M	Calf	15	1	Arteria, vena tibialis anterior Arteria, vena fibularis	Nervus peroneus profundus	Wide resection	Negative
2	68/F	Thigh	12	12	Arteria, vena femoralis	-	Wide resection	Negative
3	56/F	Thigh	8	6	-	-	Wide resection	Negative
4	56/M	Poplitea	11	12	-	-	Wide resection	Negative
5	30/F	Thigh	8	18	Arteria, vena femoralis	-	Marginal excision	Positive
6	37/F	Ankle	7 and 5: 12	24	-	-	Wide resection	Negative
7	22/M	Knee	10	7	-	-	Marginal excision	Positive

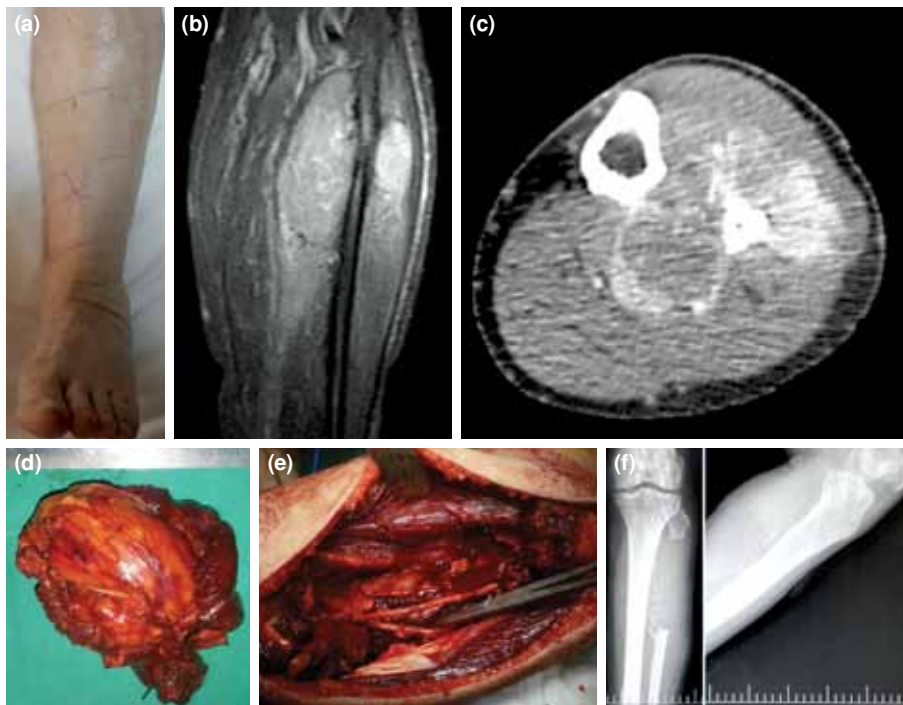


Figure 1. Proximal cruris solitary fibrous tumor. (a) Preoperative photograph of extremity. (b) Preoperative magnetic resonance coronal T2 section. (c) Preoperative computed tomography. (d) Macroscopic image of pathologic material. (e) In tumor bed, tibialis posterior over clamp and nervus tibialis inferior under clamp after (f) postoperative X-ray (Case 1).

the tumor localized to medial knee (14.2%), while one had tumor on proximal lateral cruris (14.2%) (Figures 1-3).

All patients applied with a soft tissue tumor. Mean mass size was 10.8 ± 2.4 cm (range 8-15 cm). The time passed between the symptom onset and patient application was 11.4 months (range 1-24 months) (Table I).

All patients were diagnosed via incisional biopsy. According to risk stratification, two patients were at high risk group, three patients were at medium risk group, and two patients were at low risk group (Table II).

In three patients, the tumors were closely related to vessels and nerves. Among these, one patient in high risk group with tumor localized on

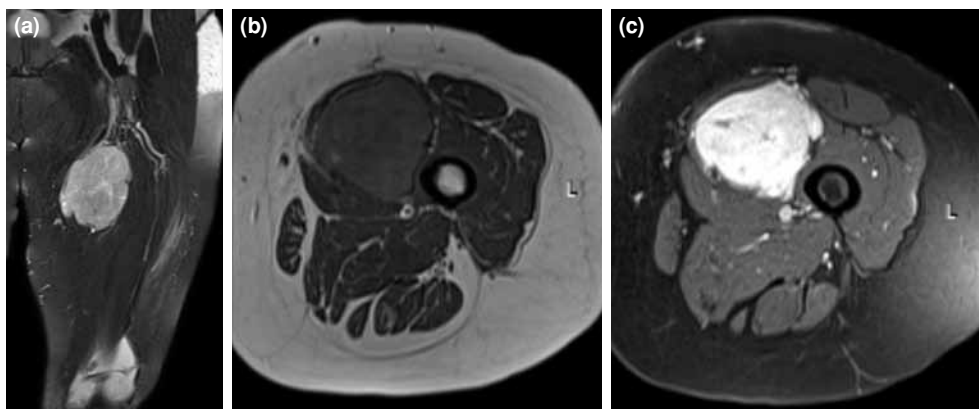


Figure 2. Solitary fibrous tumor on anteromedial thigh. (a) Preoperative magnetic resonance coronal T₂ section. (b) Preoperative magnetic resonance axial T₁ section. (c) Preoperative magnetic resonance axial T₂ section (Case 2).

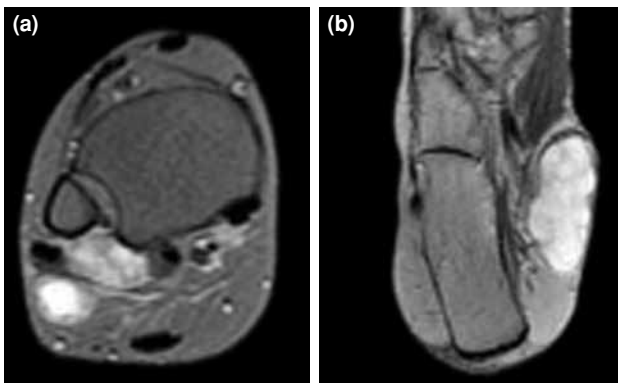


Figure 3. Solitary fibrous tumor on both medial and lateral of ankle. (a) Lateral tumor, magnetic resonance axial T₂ section. (b) Magnetic resonance medial tumor axial T₂ section (Case 6).

thigh (case 2) was performed femoral artery and femoral vein resections to establish wide resection. Saphenous vein calibration was not suitable for artery reconstruction, so polytetrafluoroethylene (PTFE) graft was administered. One patient in low risk group with tumor localized on thigh (case 5) was performed marginal excision by sparing femoral artery-vein bundles. For the patient in high risk group with tumor on proximal cruris (case 1), wide resection was performed with resection of arteria, vena, and nervus peroneus and arteria and vena tibialis anterior by sparing posterior tibial artery and tibialis posterior vein (Figure 1). Wide tumor resection was performed in other four patients.

All patients were consulted to medical oncology and radiation oncology clinics, and two patients who underwent marginal resection were also given radiotherapy. There was no chemotherapy indication for any patient (Table I).

The results of immunohistochemical staining were summarized in Table II. Histopathological evaluation belonging to SFT in thigh (case 5) was shown in Figure 4.

Chronic edema was seen in two patients (cases 1, 2), and those patients were followed-up with elevation and compression socks. One patient had acute hematoma and skin separation (case 5) and was applied hematoma drainage and suture. In one patient (case 1), foot drop was seen due to the sacrifice of peroneal nerve. Foot ankle orthosis was implanted in this patient, who tolerated it well (Table I).

After a mean postoperative follow-up period of 44 months (range 13-121 months), none of the patients had any evidence of local recurrence or distant metastasis. The follow-up and treatment of patients are still ongoing (Table II).

DISCUSSION

Solitary fibrous tumor is a pleural based rare tumor stemmed from mesenchymal cells.^[8] It is a vascular originated tumor just like hemangioma and hemangiopericytoma.^[9] Despite the fact that SFTs are localized to pleura and other serosal surfaces in general, they may nest in extrapleural soft tissues rarely.^[2] Extra-pleural SFT accounts for 0.6% of all soft tissue tumors.^[3] The World Health Organization has compiled extrapleural SFTs, hemangiopericytomas, lipomatous hemangiopericytomas and giant cell angiofibromas under extrapleural SFTs title in the classification of bone and soft tissue tumors.^[10]

Curiously, soft tissues of extremity are among the rarest site of occurrence. Most occur in the proximal lower extremity and tend to have more malignant potential.^[4] In our study, the most frequent localization was thigh as well (42.8%) and five of seven cases had malignant potential (71.4%).

Solitary fibrous tumors principally affect adults between the second and seventh decades of life (median 50 years).^[1] In the contemporary literature, there are patients that are out of this age interval (Table III).^[11,12] All patients in our study were also

TABLE II

Malignancy criteria, adjuvant chemotherapy, radiotherapy, follow-up and complications

Case	Age (year)	Tumor size (cm)	Mitosis	Total score	Risk	CT	RT	Follow-up (month)	Morbidity	Recurrence or metastasis
1	≥55	≥15	3	5	High	-	-	21	Extremity chronic edema, foot drop	-
2	≥55	10 to <15	>4	5	High	-	-	41	Extremity chronic edema	-
3	≥55	5 to <10	1	3	Medium	-	-	84	-	-
4	≥55	10 to <15	0	3	Medium	-	-	121	-	-
5	<55	5 to <10	1	2	Low	-	+	15	Acute hematoma, skin separation	-
6	<55	10 to <15	1	3	Medium	-	-	16	-	-
7	<55	10 to <15	0	2	Low	-	+	13	-	-

CT: Chemotherapy; RT: Radiotherapy.

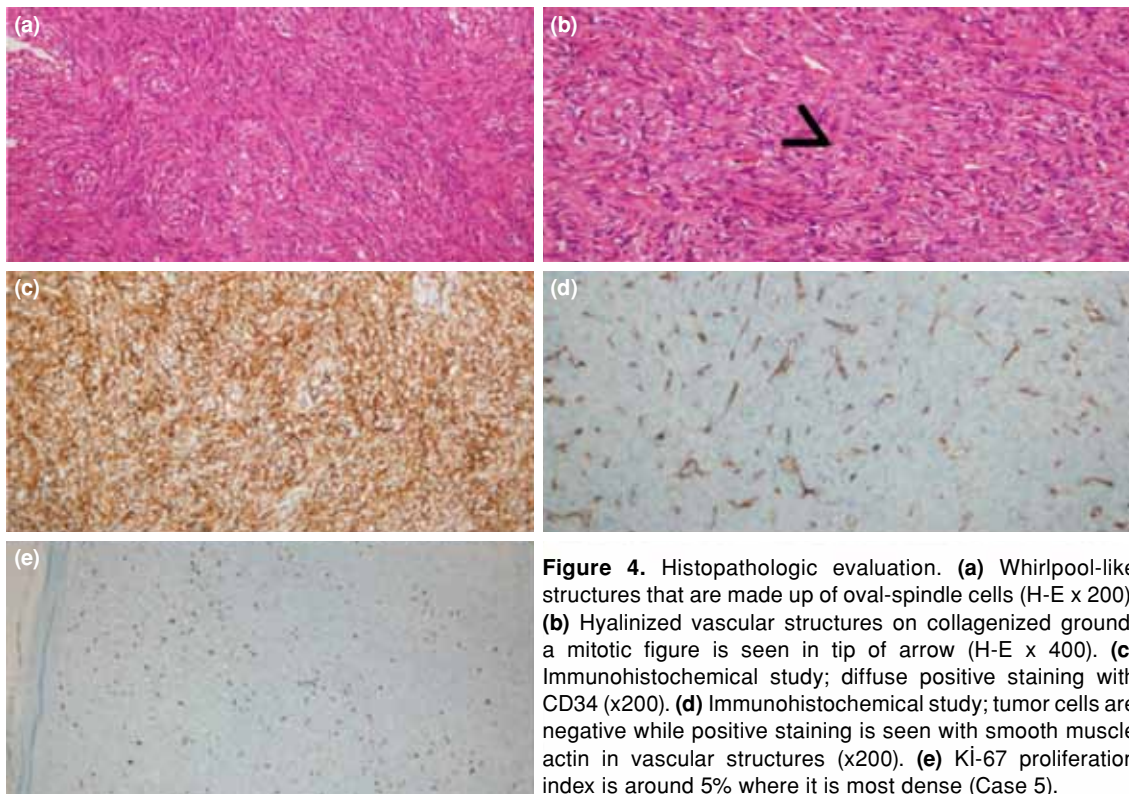


Figure 4. Histopathologic evaluation. (a) Whirlpool-like structures that are made up of oval-spindle cells (H-E x 200). (b) Hyalinized vascular structures on collagenized ground, a mitotic figure is seen in tip of arrow (H-E x 400). (c) Immunohistochemical study; diffuse positive staining with CD34 (x200). (d) Immunohistochemical study; tumor cells are negative while positive staining is seen with smooth muscle actin in vascular structures (x200). (e) Ki-67 proliferation index is around 5% where it is most dense (Case 5).

between the mentioned age interval and the mean age was 49.7 years.

Symptoms related to extrapleural SFT are relatively nonspecific and related simply to the presence of a painless mass usually in deep soft tissue.^[13] Correspondingly, all patients in our study applied with painless mass complaint.

Imaging studies like plain radiography and ultrasound are nonspecific. In MRI study, focal and diffuse severe contrast agent uptake may be seen since the tumor may have regions that are

quite vascularized. However, radiologic findings alone can not differentiate between malignant or benign tumors certainly and immunohistochemical analysis is needed to confirm the diagnosis.^[14]

The microscopic findings of SFTs are nonspecific. Tumor cells generally possess fibroblastic and myofibroblastic differentiation.^[15] Typical SFT has an irregular architecture containing various amounts of hypocellular and hypercellular areas that are rich of thick, hyalinized, branched vascular structures. Tumor cells are not atypical in general. Cellularity is changeable and mitosis is seen rarely.

TABLE III
Literature review

Authors/references	Localization	Mean age	Treatment	Follow-up (month)	Recurrence- complications
Anders et al. ^[5]	Thigh	41	Wide excision	54	-
Thanni ^[6]	Proximal cruris	22	En-bloc resection plus radiotherapy	9	Wound infection
Fukui et al. ^[10]	1 shoulder 1 thigh	81-70	Wide excision	24 - 9	-
Wan et al. ^[1]	3 thigh 1 calf	47.8	Wide excision	65.5	-
Chandanwale et al. ^[11]	Calf	15	Wide excision	12	Recurrence (12 month)
Al-Shanawani et al. ^[20]	Arm	30	Wide excision	36	-
Yoshimura et al. ^[18]	Thigh	31	Wide excision	28	Recurrence (11 month) Metastasis (19 month)
<i>Present study</i>	3 thigh 1 knee 1 calf 1 ankle 1 popliteus	49.7	2 marginal excision plus radiotherapy, 5 wide excision	44.4	2 chronic edema, 1 acute hematoma, skin separation, 1 drop foot

Malignant tumors are typically hypercellular and contain prominent atypicality, necrosis, too many mitosis ($\geq 4/10$ high power field) and irregular infiltrative margins.^[15]

In immunohistochemical evaluation, tumor cells are characteristically immunoreactive with CD34, vimentin and CD99.^[16] Variably positive reaction is seen with epithelial membrane antigen, Bcl2, and smooth muscle actin. Limited and focal reactivity with S-100 protein, cytokeratin, and desmin has been announced.^[16] Ki-67 proliferation index may be useful for determining prognosis in the evaluation of malignant SFTs.^[17]

Recent molecular studies have shown that 12q13 inversion leading to NAB2-STAT6 fusion is present in most cases.^[18]

Two types of malignant transformation have been reported; the first is the malignant or high-grade transformation from benign, low-grade, or intermediate-grade SFTs, and the second is the de novo occurrence of malignant SFTs.^[19]

Immunohistochemical patterns and some clinical indicators are used in therapeutic decisions for SFTs. According to a risk stratification model, recurrence/metastasis risk in patients was defined as low, medium, and high.^[7] Other prognostic factors are positive surgical margin and tumor size (tumor size ≥ 10 cm).^[3]

In our study, two patients were at high risk, three patients were at medium risk and two patients were at low risk groups according to histopathologic risk stratification model (Table II).

Solitary fibrous tumors in the extremities should be treated with local wide resection in patients without severe disability. If there are evidences that indicate malignant potential, wide resection together with a long-term follow-up and regular MRI controls are suggested.^[5] Recently, authors published 10 patients in whom they implemented surgical treatment and found recurrence in two patients and metastasis in one patient in spite of resection with wide margins (Table III).^[1,5,11,12,19,20]

In malignant tumors, common indications for amputation are major neurovascular involvement and large primary tumor where resection would leave a functionally useless limb.^[21]

In our study, there were involvements of femoral artery-vein in case 5 and of medial collateral ligament in case 7. There was low malignancy risk for both cases according to risk stratification model. Marginal

excision was performed for these two cases, while wide resection was performed in five cases possessing malignant potential.

Adjuvant radiotherapy and chemotherapy are recommended for metastases, recurrence and incomplete resection.^[6] Thanni^[6] has published a case in which radiotherapy was applied after en bloc resection (Table III). Two patients who underwent marginal excision in our study were applied radiotherapy (Table II).

Wide resection can be performed by means of en bloc resection in limb-sparing surgery for various malignant soft tissue tumors which are related to main vascular structures. Arterial or arteriovenous reconstruction (autologous or synthetic graft) is conducted to maintain blood flow after en bloc resection.^[22] When ipsilateral vena saphena magna, deep femoral vein junction and perigeniculate collaterals are protected, ligation of deep femoral vein does not cause any significant vascular complication.^[23]

In our study, in the patient who had SFT possessing malignant characteristics on anteromedial thigh (case 2), femoral artery and femoral vein resections were performed in order to make wide excision. Saphenous vein calibration was not suitable for artery reconstruction, so femoropopliteal PTFE bypass was conducted. Reconstruction of femoral vein could not be performed, chronic edema was seen after femoral vein ligation.

Postoperative complications are rarely seen. Wound infection was described for a case in the acute period recently (Table III).^[6] Postoperative complications in our study included chronic edema in two patients (cases 1, 2), and those patients were followed-up with elevation and compression socks. One patient had acute hematoma and skin separation (case 5), for whom hematoma drainage and suture were applied. In one patient (case 1), foot drop was seen because of sacrifice of peroneal nerve. Foot ankle orthosis was implanted to this patient, who tolerated it well. Deep venous thrombosis complication was not seen in any patients at follow-up.

The present study has several limitations. It was designed as a retrospective study, and the number of patients was limited due to the fact that the disease in question are observed rarely. The same problem occurred in other studies, as well. A multicenter study may be required to obtain a larger population.

In conclusion, in the treatment of SFT localized in extremity, marginal resection together with radiotherapy may be an alternative treatment

method for low risk group patients according to risk stratification model, for whom wide resection is not possible. Wide resection is suggested for moderate and high risk groups to decrease recurrence and metastasis risks.

Declaration of conflicting interests

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