ACTA
ORTHOPAEDICA
et
TRAUMATOLOGICA
TURCICA

Author's translation
Acta Orthop Traumatol Turc 2007;41(4):291-294

Evaluation of prognostic factors affecting recurrences and disease-free survival in extra-abdominal desmoid tumors

Ekstra-abdominal desmoid tümörlerde nüks ve hastalıksız sağkalımı etkileyen prognostik faktörlerin değerlendirilmesi

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Amaç: Tek başına cerrahi veya cerrahiyle beraber radyoterapi ile tedavi edilen primer ya da nüks ekstra-abdominal desmoid tümörlü hastalarda tedavi sonuçları ve prognostik faktörler araştırıldı.

Çalışma planı: Çalışmaya, ekstra-abdominal desmoid tümör nedeniyle tedavi edilen 38 hasta (23 kadın, 15 erkek; ort. yaş 24; dağılım 5-61) alındı. Bu hastaların sekizi (%21.1) daha önceki cerrahi sonrasında nüks gelişen olgulardı. Tümörlerin 12'si (%31.6) üst ekstremitede, 22'si (%57.9) alt ekstremitede, dördü (%10.5) aksiyel bölgede görüldü. Primer cerrahi rezeksiyon sonrasında 22 hastaya radyoterapi uygulandı. Sağkalım analizi için Kaplan-Meier yöntemi kullanıldı. Hastalar ortalama 7.3 yıl (dağılım 2.5-228 ay) takip edildi.

Sonuçlar: Tedaviden sonra 20 hastada (%52.6) nüks gelişti. Bu hastaların altısında tedavi başlangıcında da nüks vardı. Nüks gelişen 20 hastanın 11'i (%55) adjuvan radyoterapi görmüştü. Nüksler, üç hastada ilk radyoterapi bölgesinin dışında, sekiz hastada daha önce radyoterapi uygulanmış bölgede görüldü. Ortalama hastalıksız sağkalım 38±8 ay, sekiz yıllık hastalıksız sağkalım %35.7±8.5 bulundu. Ortalama hastalıksız sağkalım adjuvan radyoterapi gören (47.9±7.9 ay) ve görmeyen olgular (37.9±12.4 ay) arasında ve rezeksiyon bölgesinde nüks gelişen olgular (12.1±4.7 ay) ile farklı bölgede nüks gelişen olgular (24.3±1.0 ay) arasında anlamlı farklılık göstermedi (p>0.05). Cinsiyet, yaş, yerleşim, sınır durumu ya da radyoterapi gibi potansiyel prognostik faktörlerin hiçbiri hastalıksız sağkalım üzerinde etkili bulunmadı.

Çıkarımlar: Çalışmamızda yüksek nüks oranı ile ilişkili olabilecek herhangi bir prognostik faktör tanımlanamadı.

Anahtar sözcükler: Hastalıksız sağkalım; fibromatozis, agresif/cerrahi/radyoterapi; tümör nüksü, lokal; prognoz.

Objectives: We investigated treatment results and the role of potential prognostic factors in patients treated by surgery with or without adjuvant radiotherapy for primary or recurrent extra-abdominal desmoid tumors.

Methods: The study included 38 patients (23 females, 15 males; mean age 24 years; range 5 to 61 years) who underwent surgical treatment for extra-abdominal desmoid tumors. Of these, eight patients (21.1%) already had recurrences before treatment. Involvement was in the upper extremity in 12 cases (31.6%), in the lower extremity in 22 cases (57.9%), and in the axial region in four cases (10.5%). Twenty-two patients received adjuvant radiotherapy following surgical resection. Survival was analyzed by the Kaplan-Meier method. The mean follow-up period was 7.3 years (2.5 to 228 months).

Results: Twenty patients (52.6%) developed recurrences after treatment. Of these, recurrences were already present in six patients, and adjuvant radiotherapy was administered to 11 patients (55%). Recurrences developed at the irradiated site in eight patients, and in other regions in three patients. The mean disease-free survival was 38±8 months, and eight-year disease-free survival was 35.7±8.5%. Disease-free survival did not differ significantly between patients receiving adjuvant radiotherapy (47.9±7.9 months) and those treated with surgery alone (37.9±12.4 months), and between patients who developed a recurrence at the resection site (12.1±4.7 months) or at a different site (24.3±1.0 months) (p>0.05). None of the potential prognostic factors including gender, age, localization, surgical margin, or adjuvant irradiation were found to affect disease-free survival.

Conclusion: In our series, no prognostic factor could be identified as having an association with the high recurrence rate.

Key words: Disease-free survival; fibromatosis, aggressive/surgery/radiotherapy; neoplasm recurrence, local; prognosis.

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Submitted / *Başburu tarihi:* 12.06.2006 **Accepted / *Kabul tarihi:*** 20.09.2007

Extraabdominal desmoid tumors are locally aggressive fibrous tissue proliferations originating from musculo-aponeurotic tissues.[1] Although they lack malignant behavior such as invasion and metastatic potential, they may lead to extensive local growth and tissue invasion causing deformity, pain and eventually organ dysfunction depending on the involved area.[2-4] Desmoid tumors occur most frequently in extremities and girdles, as well as thoracic and abdominal wall. Surgery with wide local excision is the preferred treatment method. However, despite adequate margins, local recurrence is a significant problem that has been reported to range from 25% to 77% at en years.[2,5-7]

There has been considerable controversy on the role of post surgical irradiation in preventing relapse.[8-11] The relative rarity of the disease, as well as variations in presentation in treatment patterns in single institution series are potential confounding factors in determining the value of treatment strategies. Nevertheless, there is accumulative evidence on the potential benefit of radiotherapy as an adjunct to surgery both in primary and recurrent disease.[12-14]

The aim of this study is to identify prognostic factors and outcome in patients presenting with primary or recurrent extra abdominal desmoid tumors that have been treated with surgery or surgery and irradiation.

Patients and method

Between 1986 and 2005, 38(Median age was 24, ranging between 5 and 61) patients were admitted to our clinic with extra abdominal desmoid tumors. Among those who presented with recurrent disease, only eight (%22.1) with confirmed wide excisional margins at prior surgery were included in this analysis. Tumors were located at the upper extremity in 12 (31.6%) and lower extremity in 22 (57.9%) patients whereas four (10.5%) presented with axial locations.(Table 1)

All patients were treated with surgical excision. Wide margins were achieved in 30 (76.3%) patients, while the remaining three (7.9%) had microscopic and five (13.2%) had macroscopic residual disease following resection. The surgical goal at primary presentation is to achieve wide margins, while preserving limb and organ functions. Following recurrence, attempts to obtain wide and adequate margins were not compromised despite involvement of relevant neurovascular structures, in which case major surgical procedures were performed.

Adjuvant irradiation was employed in all patients presenting after 1996 as an institutional strategy, excluding skeletally immature patients for whom radiotherapy was spared for relapsed disease as an adjunct to surgery. Among 22 patients who received radiation therapy after primary surgical resection, seventeen (77.3%) had wide margins, whereas two patients (9.1%) had microscopic and three (13.6%) had macroscopic residual disease. Four patients received postoperative radiotherapy after surgery for recurrent disease (Table 1).

Following surgery adjuvant irradiation is performed at the second week postoperatively, after the removal of the wound sutures. Radiation was delivered with Megavoltage or electron beams using techniques tailored to the involved area, at a dose of 50.4 Grey 4 megavoltage with 180-200 cGy daily fractions.

Patients were followed for a median period of 7.3 years (88 months), ranging from 2.5 to 228 months. Relapse was defined as locally recurrent tumor mass evident on radiological work-up. Kaplan-Meier met-

Table 1. Patient characteristics at initial presentation

	n	%
Gender		
Male	15	39.5
Female	23	60.5
Referral		
Primary disease	30	79.0
Recurrent disease	8	22.1
Localization		
Upper extremity	12	31.6
Lower extremity	22	57.9
Axial	4	10.5
Surgical margins		
Wide margins	30	79.0
Microscopic residual disease	3	7.9
Macroscopic residual disease	5	13.2
Surgery + Adjuvant radiotherapy	22	57.9
Wide margins	17	77.3
Microscopic residual disease	2	9.1
Macroscopic residual disease	3	13.6
Prior marginal status		
Wide margins	5	62.5
Macroscopic residual disease	3	37.5

hod was used to analyze survival. Disease free survival was calculated as a time elapsed from initial surgery to first evidence of recurrence. Overall survival could not be calculated, since all patients were alive at the last follow-up. The impact of various prognostic factors on the outcome were analyzed by log-rank statistics. SPSS version 12.0 was used for all statistical evaluations.

Results

Twenty patients (52.6%) relapsed after being treated at our institution. Six of these patients were referrals from other institutions with relapsed disease on the primary resected site. Five of these relapses were localized at a different site on the same extremity, while the remaining 15 were localized at the previously resected area. Among 8 referrals with recurrence, 5 were resected with wide margins, whereas 3 had macroscopic residual disease after initial salvage surgical procedures performed at our clinic.

Among those 20 patients who relapsed, 11 of them (61.9%) had received adjuvant radiotherapy following initial surgery. Relapses occurred outside the area of prior irradiation in three patients, whereas 8 patients (76.9%) recurred within the previously irradiated area, 5 of which had wide resectional margins at primary surgery (Table 2).

In 3 patients wound enfection had arised related to radiotherapy and treated with oral antibiotherapy.

All relapsing patients underwent salvage surgical resections and seven received postoperative irradiation. Wide margins were achieved during salvage surgery in eigthteen patients, while one patient had macroscopic and one had microscopic residual disease. Median final follow-up after recurrence was 74.5 months, ranging between 2.4 and 157.9 months.

The median disease-free survival (DFS) was 38±8 months (SD 7.78; 95% CI 22.6-53.1). Eight year DFS was 35.7% ± 8.5%. Among those who presented with primary disease, the median DFS was 49 months and 8 year DFS was 46% ± 10.3%. Those with who received radiotherapy the DFS was 47.9±7.9 months; and those who didn`t receive radiotherapy it was 37.9±12.4 months($p>0.05$). There was no significant difference between the DFS rates of the patients who had recurrence at the resection site (12.1± 4.7 months) and the patients who had recurrence at a different site (24.3 ±1.0 months)($p>0.05$).

Table 2. The data of 20 relapsed patients.

	n	%
Recurrences*	20	52.6
Primary surgery	12	60.0
Recurrent referrals	6	30.0
Prior surgical margins**		
Wide margins	18	90.0
Microscopic residual disease	1	5.0
Macroscopic residual disease	1	5.0
Surgery + RT	11	55.0
Outside area of RT	3	15.0
Inside previous RT field	8	40.0

Potential prognostic factors such as gender, age, marginal status and radiotherapy did not have any significant influence on DFS. Similarly, marginal status, tumor size, gender, localization or postoperative irradiation were not shown to influence the outcome in this patient group by univariate analysis.

Discussion

This report summarizes a single institute experience over a 20-year period. Consistent with previous reports, local recurrence is the major failure pattern. Surgery is the mainstay of treatment in both the primary and relapsed settings. Recurrence rates have been reported to range between 15 and 77% .[5,7,15-17]

In our series, with primary presentation, recurrence rate at eight years is 52.6%. Due to the limited sample size, we were unable to identify any prognostic factors that may have accounted for the high relapse rate. Wide resections with negative margins have generally been correlated with lower recurrences.[10,12,16,18,19] A reasonable explanation for this indiscrepancy is that desmoid tumors may extend through fascial planes among muscle bundles, limiting a reliable estimate of the disease extent during surgery. A second reason is the reluctance to perform a mutilating surgery in a benign setting that prefers to encircle major neurovascular structures. This has led to considerable controversy on what defines wide margins.[16] Nevertheless; marginal status has not been consistently associated with improved local control.[17,20]

In this study most of the patients (6/8) who had presented with recurrent disease suffered from relapse at a later period. This shows that contamination due to inadequate surgery influences success rates of

the secondary operation and primary surgical operation is an important factor for prognosis.

Postoperative irradiation has resulted in a non-significant trend towards longer DFS in our patient group (median 48 versus 38 months). The role of adjuvant radiotherapy has been a matter of ongoing debate in studies addressing this issue. There are data suggesting that postoperative irradiation is beneficial in disease control,[21] whereas some have not been able to show any benefit.[20,21] A comprehensive evaluation on radiotherapy by Nuyttens et al.[14] have shown significantly increased local control with adjuvant irradiation after surgery. In general, investigators have adopted the strategy of employing postoperative radiotherapy in resections with close or microscopically positive margins.[10,16] The limited sample size in our series precludes us to reach clear cut guidelines on the treatment of desmoid tumors. Despite the lack of randomized data, surgery with the intent to get tumor free margins has gained general acceptance among clinicians. Postoperative irradiation may provide benefit in patients with microscopic or macroscopic residual tumors, as well as relapsed disease.

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