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Radiotherapy in desmoid tumors

Treatment response, local control, and analysis of local failures

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Abstract

Background Desmoid tumors (aggressive fibromatosis) are rare soft tissue tumors which frequently recur after surgery. Desmoid tumors arise from musculoaponeurotic tissue in the extremities, head and neck, abdominal wall, or intra-abdominally. Our aim was to examine the outcome of radiotherapy of desmoid tumors in a single institution series. **Patients and methods** We evaluated 41 patients with desmoid tumors treated with 49 radiotherapies between 1987 and 2012. Radiologic images for response evaluation were reassessed and responses to treatment registered according to RECIST criteria 1.1. For patients with local failures radiation dose distribution was determined in each local failure volume using image co-registration. Recurrences were classified as in-target, marginal, or out-of-target. Prognostic factors for radiotherapy treatment failure were evaluated.

Results Radiotherapy doses varied from 20–63 Gy (median 50 Gy) with a median fraction size of 2 Gy. The objective response rate to definitive radiotherapy was 55% (12/22 patients). Median time to response was 14 months. A statistically significant dose-response relation for definitive and

postoperative radiotherapy was observed both in univariate (p -value 0.002) and in multivariate analysis (p -value 0.02) adjusted for potential confounding factors. Surgery before radiotherapy or surgical margin had no significant effect on time to progression. Nine of 11 (82%) local failures were classified as marginal and two of 11 (18%) in-target. None of the recurrences occurred totally out-of-target.

Conclusions Radiotherapy is a valuable option for treating desmoid tumors. Radiotherapy dose appears to be significantly associated to local control.

Keywords Aggressive fibromatosis · Radiotherapy · Local recurrence · Dose-response relationship, radiation

Radiotherapie bei Desmoid-Tumoren

Therapieansprechen, lokale Kontrolle und Lokalrezidivbewertung

Zusammenfassung

Hintergrund Desmoide (aggressive Fibromatosen) sind seltene Weichteiltumore der muskulären Membranen von Kopf, Hals, Extremitäten und Bauchwand. Ziel war es, die Wirksamkeit der Strahlentherapie bei aggressiver Fibromatose an einer einzelnen Klinik zu untersuchen.

Patienten und Methode Ausgewertet wurden 41 Patienten mit aggressiver Fibromatose, die zwischen 1987 und 2012 mit 49 Strahlentherapien behandelt wurden. Das Ansprechen wurde anhand der radiologischen Aufnahmen neu beurteilt und der Behandlungserfolg gemäß RECIST-1.1-Kriterien registriert. Für Patienten mit Lokalrezidiv wurde die Dosisverteilung der Radiotherapie durch Fusion von diagnostischen CT- und MRT-Bildern mit den Planungs-CT-Aufnahmen für jedes Lokalrezidiv bestimmt. Die Rezidive wurden je nach Lage eingeteilt in: innerhalb, am Rande und

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außerhalb des ehemaligen Bestrahlungsvolumens gelegen. Prognostische Faktoren für ein Therapieversagen wurden ausgewertet.

Ergebnisse Die Gesamtdosen der Strahlentherapie lagen zwischen 20 und 63 Gy (Median 50 Gy) mit einer medianen Fraktionierung von 2 Gy. Die objektive Ansprechrates war 55 % (12/22 Patienten). Die mediane Zeit bis zum Therapieerfolg betrug 14 Monate. Eine statistisch signifikante Dosis-Wirkungs-Beziehung für die definitive und die postoperative Strahlentherapie wurde sowohl in der univariaten (p -Wert 0,002) als auch in der für potentielle Störfaktoren korrigierenden multivariaten Analyse (p -Wert 0,02) beobachtet. Neun von 11 (82 %) Lokalrezidiven wurden als Felddrandrezidive und zwei von 11 (18 %) als innerhalb des Bestrahlungsfelds liegende Rezidive bewertet. Kein Lokalrezidiv trat komplett außerhalb des Bestrahlungsfelds auf. **Schlussfolgerung** Die Strahlentherapie ist eine wertvolle Therapiewahl zur Behandlung aggressiver Fibromatosen. Die Strahlentherapiedosis hat einen signifikanten Einfluss auf die lokale Kontrolle.

Schlüsselwörter Aggressive Fibromatose · Radiotherapie · Lokalrezidiv · Dosis-Wirkungs-Beziehung, Bestrahlung

Introduction

Desmoid tumors are locally aggressive nonmalignant soft tissue tumors which may recur after radical surgery. Desmoid tumors are often asymptomatic but may cause pain, stiffness, and function loss when compressing and infiltrating adjacent structures. The majority of desmoid tumors are sporadic without a genetic predisposition [1]. Familial adenomatous polyposis (FAP) carriers have an increased risk as approximately 20% of FAP carriers develop desmoid tumors [2]. Other risk factors are pregnancy and physical or surgical trauma. It is possible that growth factors associated with tissue healing may induce desmoid tumor growth [3]. Fatal outcomes have predominantly been reported in FAP patients with mortality rates up to 13% [4].

The optimal treatment of desmoid tumors is still controversial. Spontaneous regression has been reported in 4–28% of patients with the highest rate recorded in abdominal wall tumors [5–8]. The National Comprehensive Cancer Network guidelines recommend a careful “wait and see” approach if the tumor is asymptomatic and not located in an area that could lead to functional limitations if the tumor increases in size. If progression occurs, desmoid tumors can be treated with surgery and/or radiation therapy and/or systemic therapy [9–11]. The role of preoperative or postoperative radiotherapy (RT) is at least as controversial as

that of surgery [12]. Local relapse, young age, large tumor size, intra-abdominal or extremity location, or mutation 45F in the β -catenin gene *CTNNB1* have been reported to increase the risk for recurrence [13–15]. When radical surgery is not possible or would cause notable functional impairment or mutilation, definitive RT or systemic treatment have been reported to benefit for symptomatic patients. Systemic treatment options such as chemotherapy, hormonal agents, nonsteroidal anti-inflammatory drugs, and tyrosine kinase inhibitors have shown some efficacy but there are no randomized controlled trials [10].

Our aim was to examine the outcome of RT of desmoid tumors in a single institution series. In order to assess RT target margins and dose-response, we analyzed local failures after RT and determined the prior radiation dose at the site of local failure. To our knowledge such failure analysis has not been previously reported in desmoid tumors. Similar studies have been proven useful in e. g. head and neck cancers and soft tissue sarcomas [16, 17].

Methods

Patients

Our sarcoma group treated 136 desmoid tumor patients including 45 patients treated with RT between 1987 and 2012. Six RTs in 4 patients (two postoperative and four definitive RTs) were excluded because of inadequate or lost imaging for response evaluation, simultaneous systemic therapy or short (<6 months) follow-up. Thus, the present study includes 41 adult desmoid patients treated for 44 different tumors with 49 courses of RT (Supplementary Fig. 1). Clinical data were retrieved from patient records and survival data were obtained from the Population Register Center. Patient and tumor characteristics are summarized in Table 1. The ethics committee of Helsinki University Hospital and the Ministry of Health and Social Affairs approved the study. The study was conducted in accordance to the current version of the Helsinki Declaration.

An experienced sarcoma pathologist (M.R.) re-examined the tumor specimens and confirmed the histology for all 41 patients. A radiologist (A.B.) and three oncologists (M.T., C.B. and K.S.) reassessed the radiologic images (CTs and MRIs) for response evaluation according to modified RECIST criteria 1.1 including only patients with measurable disease [18].

Dose distribution analysis

A physicist (L.T.) in cooperation with a radiologist (A.B.) and oncologists (C.B. and K.S.) analyzed the local failures to investigate the RT dose distribution. All patients with

Fig. 1 Time to progression in 43 desmoid tumors treated with 47 RTs and divided according to the RT dose. Total number of local failures was eleven. Two RTs were excluded from this analysis due to incomplete imaging. *RT* radiotherapy

Table 1 Clinical characteristics of 41 patients and 44 tumors treated with 49 radiotherapy courses

<i>Age at diagnosis</i>	
<30	10
30–60	20
>60	11
Median age at diagnosis (range)	45 (5–79)
<i>Female</i>	
Male	28
<i>Male</i>	
FAP	13
FAP	4 (10%)
Median size of the primary tumor (range), cm ^a	8 (2–26)
<i>Site</i>	
Trunk	14 (34%)
Extremities	21 (51%)
Head and neck	2 (5%)
Multicentric	4 (10%)
Prior trauma	8 (20%)
<i>Surgery and margins</i>	
Negative margins	5 (10%)
Positive margins	21 (43%)
No surgery	23 (47%)
Median follow-up time, years (range)	7 (0.8–17)

FAP familial adenomatous polyposis

^aThe size of six tumors could not be found from the original data nor reanalyzed

a relapse had a CT-based planning performed according to ICRU 50 criteria. The diagnostic MR/CT images were imported into the treatment planning system (Eclipse® 11.0, Varian Medical Systems Inc., Helsinki, Finland). The recurrence volumes were contoured in the diagnostic MR/CT images, followed by a manual rigid co-registration with the RT planning CT using bony landmarks and visible soft tissue structures in the immediate surroundings of the recurrence. The contoured recurrence volumes were copied into the planning CT and dose-volume histograms were generated. A treatment failure was classified in-target if $\geq 95\%$ of the recurrence volume occurred within the volume receiving $\geq 95\%$ of the prescribed radiation dose. A treatment failure was classified marginal if the recurrence volume border crossed the 95% isodose and less than 95% of the relapse volume was located inside the volume receiving $\geq 95\%$ of the radiation dose. The failure was classified as out-of-target if it was completely outside the 95% isodose of the target volume [19].

Treatments

The aim of surgical treatment was complete resection of the desmoid with free margins without excessive morbidity or mutilation. Postoperative RT was offered to patients considered to have a high risk of recurrence because of positive ($n = 22$) or narrow margins ($n = 4$). If an operation was assessed too mutilative, definitive RT was considered for progressing and/or symptomatic tumors. RT was delivered with healthy tissue margins and patients' fixation was tailored individually. RT details are listed in supplementary Table 1.

Statistics

SPSS Statistics version 22 was used for statistical analysis. Kaplan–Meier model was used for survival curves and recurrence rate. Univariate and multivariate analysis of factors related to time to progression was done with Cox regression. A two-sided p -value < 0.05 was considered statistically significant.

Results

The median follow-up time for survival was 7 years (range from 9 months to 17 years). One pleomorphic undifferentiated sarcoma developed inside previously irradiated volume after a 9-year interval. This RT-induced malignancy was excised and the patient remained free of disease during the 6-year follow-up. No other serious RT sequelae were found.

Table 2 Univariate and multivariate analysis of tumor and patient characteristics and time to progression

Characteristic	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> -value	HR	<i>p</i> -value
Age, years	0.98 (0.9–1.0)	0.18	1.00 (0.9–1.0)	0.73
Sex ^a	1.43 (0.4–4.7)	0.55	1.34 (0.3–5.6)	0.69
FAP ^b	2.03 (0.4–9.8)	0.38	0 (0–1.3)	0.06
Tumor size, cm	1.05 (1.0–1.2)	0.28	1.05 (0.9–1.3)	0.58
Location ^c	1.70 (0.5–5.6)	0.39	1.41 (0.3–6.6)	0.66
Recurrence after surgery ^d	0.58 (0.2–1.9)	0.37	0.62 (0.1–3.4)	0.59
Surgical margin ^e	0.55 (0.2–1.4)	0.22	0.48 (0.2–1.5)	0.20
RT dose, Gy	0.91 (0.9–1.0)	0.002	0.71 (0.5–0.9)	0.02

FAP familial adenomatous polyposis, RT radiotherapy, HR hazard ratio

^a1 = female, 2 = male

^b1 = no, 2 = yes

^c1 = extremities, 2 = other

^d1 primary, 2 recurrence after surgery

^e0 = RT only, 1 = positive, 2 = negative margins

Objective response to definitive RT in patients with macroscopic disease

Doses in 22 RTs varied from 20–63 Gy (median 50 Gy) and the fractions from 1.8–2.1 Gy (median 2 Gy). Estimated local control was 62% at 5 years. A complete response was seen in three tumors (14%), a partial response in nine (41%) and stable disease in ten tumors (45%). The objective response rate was 55% (12/22) with no direct disease progression at 6 months. Median time to response was 14 months (range from 4–38 months). The duration of the response to RT ranged from 6 months to 12 years (median 30 months) (Appendix). The median time to progression in the five tumors progressing was 4 years (range from 9 months to 5 years).

Time to progression after definitive or postoperative RT and analysis of prognostic factors

Estimated local control in 47 RTs was 75% at 5 years and 65% at 10 years. The median time to progression in patients experiencing a recurrence was 22 months (range from 9 months to 6 years). The impact of surgery, surgical margins, RT dose, FAP, tumor size, location, age, and sex on time to progression (TTP) was studied in univariate and multivariate Cox regression models. The results are shown in Table 2. RT dose was the only factor which had a significant impact on TTP. The significant impact of RT dose remained in a per patient analysis in Cox multivariate analysis ($p = 0.04$). Doses under 50 Gy yielded a local control rate of 57% (4/7), doses from 50–59.9 Gy 75% (24/32), and doses equal to or greater than 60 Gy 100% (8/8) (Fig. 1). Re-analysis using equivalent total dose gave similar results in both univariate ($p = 0.001$, hazard ratio (HR) = 0.91) and multivariate analysis ($p = 0.023$, HR = 0.68). RT dose

was significantly associated to TTP after definitive RT ($p = 0.047$, HR 0.92) but not after postoperative RT, even if the hazard ratio in this group was lower ($p = 0.16$, HR 0.83). Surgical margin had no significant effect on TTP in univariate or multivariate models.

Analysis of local failures after RT utilizing image fusion

We evaluated the locations of local failures in 11 RTs in relation to the previous irradiated volume (Supplementary Table 2). Ten tumors, of which one was irradiated twice, were irradiated in 10 patients. A boost was delivered to four of these tumors. Five failures were recurrences after postoperative RT (total doses 45–60 Gy (median 50 Gy) with fractions from 1.8–2 Gy) and six after definitive RT (total doses 30.6–50 Gy (median 50 Gy) with fractions from 1.8–2 Gy). Two failures were classified as in-target (doses 50 Gy in 2 Gy fractions and 45 Gy in 1.8 Gy fractions), nine were marginal. No out-of-target failures were encountered. In the 4 patients given boost, the failure was marginal in two and in-target in one tumor. One recurrence was classified as marginal in relation to the initial 50 Gy volume and out-of-target in relation to the 10 Gy boost volume.

Discussion

A conservative watchful waiting approach has been proposed as the first choice in the management of desmoid tumors due to the relatively high frequency of spontaneous regression [20]. Radical surgery is the mainstay of treatment in progressing or symptomatic patients. Many desmoid patients are young and therefore RT is usually recommended only if radical surgery is impossible or would cause notable mutilation or functional impairment. The results of

the present study indicate that RT is a valuable option for treating desmoid tumors.

More than a half of the patients experienced an objective response to RT in the current material which is more than could be expected due to spontaneous regression. Achieving a response to RT may take from months to years. In the current study objective measurable responses were reached after a median of 14 months. None of the patients progressed immediately after RT. The 10-year local control was 65% and the last progression occurred after more than 6 years of follow-up. The time to first evidence of objective response was long as was the time to progression in patients with local failures. This illustrates the slow clinical course of the disease.

According to a review RT treatment failures in desmoid tumors have occurred in-field in 54% of patients and marginally in 30% but out-of-field in only 16% [21]. In the current study the location of treatment failure was classified as marginal in the majority of patients and in contrast to previous literature only a few were in-target. Similar outcomes as in the current study have also been observed [22]. To our knowledge none of the prior desmoid studies have used image fusion of treatment planning and diagnostic images to classify the site of failures relative to the RT dose distribution. Thus, the definition of the failure location differs from previous studies. An in-field recurrence is not always in-target since a relapse is classified marginal if only a portion of the tumor received a full dose. This might explain the higher number of marginal recurrences in our study. Moreover, in previous studies the locations of the recurrences have been recorded without a precise definition [15, 21, 23]. Our results agree with previous findings with rare out-of-target recurrences. The pattern of recurrence in this series contrasts with our experience in malignant soft tissue tumors where the vast majority of recurrences were seen in-target [17]. The growth pattern of desmoid tumors may explain the difference as approximately half of desmoid tumors have infiltrative margins and often extend along fascial planes [24]. A wide safety margin of 5–7 cm is recommended in RT for desmoid tumors [15]. This recommendation is supported by our findings that recurrences occurred mainly marginally. The results might improve with MRI-based RT treatment planning since desmoid tumors are usually better visualized in MRI than in CT [25].

Yao et al. [26] conducted a systematic review of 22 articles comparing surgery and RT from 1990–2012 and reported that the long-term local control with surgery plus RT or RT alone in studies with at least 5-year median follow-up varied from 25–100% with a median of 78%. The local control of 77% in the current study is in line with these findings. Combining surgery with RT yielded a higher local control rate than surgery alone in three out of five stud-

ies with a multivariate analysis [27–29]. Two studies that compared the combination treatment to definitive RT found no difference between the groups [15, 30]. These results are supported by our findings. Keus et al. [31] performed a prospective phase II study of RT for inoperable desmoid tumors with an objective response rate of 50% at 3 years with a dose of 56 Gy in 2 Gy fractions. Our results are remarkably similar with an objective response rate of 55%. The longest time to achieve an objective response was over 3 years for 2 patients in the present study while Keus et al. reported three responses detected after 3 years. Many desmoid tumors grow slowly and the time to response seems to be equally slow.

Several prognostic factors for recurrence after RT have been identified in previous studies. Surgical margin, RT in addition to surgery, age, sex, tumor size, and presentation status (primary or recurrent) have been found to be associated with recurrences [15, 27, 28, 32]. Unlike previous studies we found no association between any of these factors to recurrence after RT. One reason for this may be differences in patient characteristics, i. e., inclusion of only irradiated patients in the present study, the relatively small size of our study another. RT dose was the only factor significantly associated with local control. Several previous studies have shown evidence of dose-response relationship in desmoid tumors with higher local control for RT doses exceeding 50 Gy, mainly in treatment of macroscopic disease [21, 33, 34]. Other studies, however, have failed to establish a significant dose-response [15, 22, 23, 35]. Most studies with a dose-response analysis have been relatively small especially considering RT alone with the largest single study hitherto comprising 41 patients [15]. The difficulty to document a dose-response in microscopic disease may be due to several factors. First, in microscopic disease the local control rate may be higher and the events may remain too few for a meaningful dose-response analysis. Second, the dose necessary to eradicate the tumor cells may be lower in microscopic disease. Our results in combination with the previous studies endorse a positive dose-response in desmoid tumors. Previous data support RT doses ≥ 50 Gy and the recommendation of 50 Gy dose for postoperative RT and 56 Gy for macroscopic tumors holds a radiobiological basis [15, 26]. Doses higher or equal to 60 Gy have been proposed for definitive RT with improved local control rates of 80 and 88%, but these findings have not been confirmed in more recent analyzes and the optimal dose remains to be determined [15, 28, 35, 36]. Moreover, the elevating risk of RT-related complications, including rare secondary malignancy, should be taken into account when prescribing the treatment especially since many patients are young [29].

The incidence of desmoid tumors in Finland is 2.4–4.3 per 1000000 annually which is similar to other reported in-

cidence rates [37]. With a 5.4 million population, the number of desmoid tumors should approach 400 within the 26-year study period. The Hospital District of Helsinki and Uusimaa comprises less than a third of the Finnish population and only a small proportion of the patients receive oncological treatments. As our center serves as a national reference center, our patient collective may have tumors that are more difficult to treat. This might also be reflected in our treatment results. Other limitations of the current investigation include retrospectivity and the long study period resulting in RT delivery with heterogeneous techniques and doses.

Conclusion

The present study shows that RT is a valuable option in progressing desmoid tumors not amenable to surgery or when surgery might lead to unacceptable mutilation. Previously the optimal dose of RT in desmoid tumors has not been defined. A significant dose response in the present study suggests that higher doses than previously prescribed may be optimal. Validation of this result in a larger patient collective and in a prospective study would be desirable due to the retrospective nature of the study. All patients received RT in this study and we did not find any impact on the extent of previous surgery. When surgery with clear margins is not achievable in progressive desmoid tumors definitive RT should be preferred.

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Compliance with ethical guidelines

Conflict of interest K. Santti, A. Beule, L. Tuomikoski, M. Rönty, A.-S. Jääskeläinen, K. Saarilahti, H. Ihalainen, M. Tarkkanen, and C. Blomqvist declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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