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Annals of Oncology

Annals of Oncology 24: 2672–2676, 2013
doi:10.1093/annonc/mdt254
Published online 17 July 2013

Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis—an EORTC STBSG and ROG study (EORTC 62991–22998)

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Received 17 April 2013; revised 29 May 2013; accepted 31 May 2013

Background: To determine the activity of radiotherapy in patients with inoperable desmoid-type fibromatosis (DF) a multicenter prospective phase II trial was carried out.

Materials and methods: Patients with inoperable progressive disease of primary, recurrent or incompletely resected lesions received a dose of 56 Gy in 28 fractions. Follow-up MRI studies were carried out every 3 months for 2 years and thereafter every 6 months. The primary end point was local control rate at 3 years, estimated by a nonparametric method for interval-censored survival data. Secondary end points were objective tumor response, acute and late toxic effect.

Results: Forty-four patients (27 F/17 M) were enrolled from 2001 to 2008. Median age was 39.5 years. Main tumor sites included trunk 15 (34.1%) and extremities 27 (61.3%). Median follow-up was 4.8 years. The 3-year local control rate was 81.5% (90% one-sided confidence interval 74% to 100%). Best overall response during the first 3 years was complete response (CR) 6 (13.6%), partial response (PR) 16 (36.4%), stable disease 18 (40.9%), progressive disease 3 (6.8%) and nonassessable 1 (2.3%). Five patients developed new lesions. After 3 years, the response further improved in three patients: (CR 2, PR 1). Acute grade 3 side-effects were limited to skin, mucosal membranes and pain. Late toxic effect consisted of mild edema in 10 patients.

Conclusions: Moderate dose radiotherapy is an effective treatment of patients with DF. Response after radiation therapy is slow with continuing regression seen even after 3 years.

Key words: desmoid-type fibromatosis, aggressive fibromatosis, desmoid tumors, radiotherapy, soft tissue tumors

introduction

Desmoid-type fibromatosis (DF) previously known as aggressive fibromatosis and musculoaponeurotic fibromatosis is a rare soft tissue neoplasm with a typical clinical behavior of frequent local recurrences and absence of distant spread [1]. The growth pattern is infiltrative and nonencapsulated which explains the tendency for local recurrence especially after marginal or intralesional excision. Despite the local behavior of these tumors, the survival prognosis remains good. However, frequent recurrences and subsequent treatment sequelae can considerably hamper the functional outcomes and quality of life, as well as cause life threatening events at certain locations. Other characteristics of this disease are an age peak between 30 and 40 years, and female predominance often with pregnancy-associated abdominal wall lesions. Mesenteric lesions are frequently seen in patients with an APC gene mutation as in familial polyposis coli (Gardner's syndrome) [2]. Both mutations in the APC gene and activation of the Wnt/beta-catenin pathway result in elevated levels of intracellular beta-catenin, which seem to play a role in the molecular pathogenesis of DF [3]. Further studies of these mechanisms might lead to future therapeutic strategies [4].

Surgery is usually the first line of treatment. Wide surgical excision of the tumor is the recommended treatment procedure. Reported local recurrence rate after primary surgery differs considerably [5]. The biological natural behavior of DF can be unpredictable and variable. A significant proportion of patients

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have tumors that remain spontaneously stable after a period of growth or even regress and hence benefit from a front-line nonaggressive policy (watch-and-wait) [6].

Frequently only patients who experience multiple recurrences are referred for nonsurgical treatment. Retrospective data from several published series support the role of postoperative radiotherapy in preventing progression or reducing the incidence of local recurrence in case of recurrent tumors or resected tumors with involved surgical margins [7–9].

Radiotherapy alone as a treatment modality for this disease has been used in a few series of limited size [8, 10, 11]. In these series, the authors report slow regression and prolonged progression-free interval. Nuyttens et al. pooled the reports from the literature [8]. A total of 102 patients were identified who were treated with radiotherapy only, most patients receiving a dose between 50 and 60 Gy. In 80 of 102 (78%) of these patients, local control was obtained.

To date, no other treatment modality has shown similar good results although recent reports with targeted drugs show promising data [12, 13].

This trial was designed to confirm the role of moderate doses of radiotherapy in bulky inoperable and progressive disease or in case of expected extensive and mutilating surgery.

materials and methods

study design and patient eligibility criteria

This multicenter phase II study was carried out by the Soft Tissue and Bone Sarcoma Group and the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer (EORTC). Ten centers entered 44 patients between 13 November 2001 and 2 April 2008.

Eligibility criteria were age 16 years or older, histologically confirmed DF arising in any site in one of two categories: (i) patients with primary disease or with recurrent disease after prior complete remission or complete resection or patients with progressive disease after any prior treatment not including radiotherapy, that is either inoperable, or requiring major surgery resulting in an anticipated large functional or cosmetic deficit or mutilation and (ii) patients with incompletely resected tumor who had gross residual disease not suitable for further surgery and whose first surgery was carried out within 3 months from registration. All patients had to have measurable disease as defined by RECIST 1.0. Documentation of progressive disease was required for all patients, except for patients with recurrent disease, or with incompletely resected tumor within 3 months from registration. Progression was defined as at least 20% increase of the longest diameter of the target lesion documented on two MRI scans carried out not more than 1 year apart. Patients were to have a lesion suitable for radiation therapy, according to the protocol. Patients with bulky intra-abdominal disease in close relation with small bowel were not eligible.

Prior surgical, endocrine therapy or chemotherapy was allowed but no concurrent endocrine or chemotherapy was permitted. No prior radiotherapy to the indicator lesion and no prior or concurrent isolated limb perfusion with TNF were allowed. Pathological material had to be available for central review and was classified according to the 2013 WHO criteria [1].

The trial was approved by the institutional review board of each participating institution. All patients gave written informed consent.

study design and treatment plan

The target volumes were defined in agreement with ICRU Report 50 by clinical information, CT scan and/or MRI. The gross target volume (GTV) encompassed the entire known tumor. The clinical target volume (CTV) was defined as the GTV with a margin to allow for suspected microscopic spread. This margin was at least 5 cm in longitudinal direction following the muscle fibers of the compartment in which the lesion is located and 2 cm in other directions. In tumors without a clear relation to a specific muscle compartment, a margin of 2 cm in all directions was used. The planning target volume (PTV) was obtained by expanding the CTV with a margin to allow for setup uncertainties and organ movement. This extra margin depended on anatomical site and the utilized mobilization and treatment technique was typically 0.5–1 cm. The protocol required a treatment plan individually customized to the anatomical site and size of the target volume. For superficial lesions, electron beams were used while for other tumor sites, multiple photon beam techniques were used to achieve the required dose distribution. Brachytherapy was not allowed in this study. Verification portal films were made before the delivery of radiotherapy. A dose of 56 Gy in 28 fractions, 2 Gy per fraction, 5 fractions per week was prescribed to the target volume. In head and neck and extremity cases, it was recommended to use immobilization devices to maintain the same position for all planning and treatment procedures.

patient evaluation

Before treatment, a baseline MRI was mandatory for all patients. Post completion of treatment patients were followed for at least 5 years. A clinical evaluation was carried out every 3 months for 2 years and thereafter every 6 months. MRI investigations were carried out at 3, 6, and 12 months after the end of treatment and thereafter each year up and until 5 years. RECIST criteria were used for the determination of progression at 3 years and for the determination of response to therapy. Toxic effect evaluation was assessed using the International Common Toxicity Criteria scale for acute side-effects (CTC version 2.0). Acute side-effects were evaluated weekly during therapy. Late side-effects were assessed using the RTOG-EORTC late morbidity scale as described in the CTC document. Tumor material was centrally reviewed.

statistical analysis

A Fleming phase II one-step design was used in this study. The primary end point was absence of local progression (local control) rate measured 3 years after registration. To be able to distinguish a treatment warranting further investigation (characterized by a 3-year local control rate of 70%) from a treatment with insufficient activity (characterized by a 3-year local control rate of 50%), with alpha (one-sided) of 0.10 and 90% power, a total of 38 patients followed for at least 3 years were required.

Due to a high drop-out rate, the 3-year local control rate was estimated by a nonparametric method for interval censored survival data [14]. In this analysis, the time to local progression was counted from the date of registration until the (unknown) date of the first local progression which is assumed to occur in the time interval between the last clinical visit before and the first visit at which the local progression was observed (or infinity if the event was not observed).

The criterion for success was to demonstrate that the one-sided 90% confidence interval (CI) around the 3-year local control rate estimate is above 50%. This analysis was carried out in the intent to treat population.

Statistical analyses were done with SAS (version 9.2). The clinical cut-off date used for the final analysis was 27 February 2012.

The study was registered with ClinicalTrials.gov, number NCT00030680.

results

Forty-four patients were entered in the study (27 F/17M). The median age was 39.5 years (range 17.7–73.7 years). Table 1 shows demographics and baseline characteristics. The DF was in

Table 1. Patient and tumor characteristics

	All patients ($n = 44$)
Sex	
Male	17 (38.6%)
Female	27 (61.4%)
Age (years)	
≤20	1 (2.3%)
20–29	12 (27.3%)
30–39	10 (22.7%)
40–49	8 (18.2%)
50–59	9 (20.5%)
>60	4 (9.1%)
Median (years)	39.5
Range	17.7–73.7
Disease category	
Primary	17 (38.6%)
Recurrent	17 (38.6%)
Progressive	6 (13.6%)
Incomplete resection	4 (9.1%)
Histopathology review	37 (84.1%)
Desmoid-type fibromatosis	35 (95.6%)
Other histopathology	2 (5.4%)
Site of tumor	
Neck	1 (2.3%)
Thoracic wall	10 (22.7%)
Abdominal wall	5 (11.4%)
Pelvis	1 (2.3%)
Lower extremity	13 (29.5%)
Upper extremity	14 (31.8%)
Time from the first diagnosis	
Median	11.8 months
Range	1 day to 27.2 years
Prior therapy	
Radiotherapy	2 (4.5%)
Surgery	26 (59.1%)
Chemotherapy	5 (11.4%)
Endocrine therapy	4 (9.1%)
Largest diameter (mm)	
<40	9 (20.5%)
40–79	19 (42.2%)
80–119	4 (9.1%)
≥120	12 (27.3%)

general a primary or recurrent tumor (77.2%). Six (13.6%) patients had progressive disease after prior treatment and four (9.1%) were included following incomplete resection. The majority of patients (61.3%) had a tumor located in the extremities. The median time since the first diagnosis was around 1 year with a range of 1 day to 27 years. Previous treatment consisted of surgery in 59.1% of patients, and 4% had previous radiotherapy at another site. Nine percent received endocrine therapy and 11% received chemotherapy. Twenty-nine of 44 patients (66%) received at least one prior treatment. An independent pathologist reviewed 37 patients for whom tumor material was available. Two out of these were not considered as DF, but identified as a sclerosing epithelioid fibrosarcoma and a desmoplastic fibroblastoma. Additionally, one patient was ineligible because of starting treatment before registration, making a total of three ineligible patients.

Of the 44 patients who started the allocated treatment, 42 completed treatment as planned and received 56 Gy in 28 fractions. Two patients stopped treatment early; one due to excessive skin toxic effect (at 54Gy) and one had a planned dose reduction (50 Gy) due to concerns about brachial plexus toxic effect. Temporary interruption of treatment was reported in four patients, three due to skin toxic effect and one due to an unrelated medical event.

The irradiation technique used was a photon beam plan in 40 patients, three were treated with electrons, and one had a mixed photon electron technique.

The final analysis was carried out with a median follow-up of 4.8 years.

Ten patients developed local progression: eight patients during the first 3 years and two between 3 and 5 years after start of treatment. The 3-year local control rate was estimated by interval censored survival analysis to be 81.5% (90% one-sided CI 74% to 100%) (Figure 1). As the lower bound of the CI is above 50%, the protocol hypothesis is met. We had the same conclusion in the per protocol set or when adjusting for competing risk (results not shown but available from author).

Objective response to therapy was evaluated on the basis of lesions included in the irradiation field. During follow-up, five patients developed new lesions. In three of these, simultaneous progression was detected in the target lesion. One new lesion was located in the radiotherapy field and one patient developed a new lesion outside the radiotherapy field without local progression. Best overall response during the first 3 years after start of treatment of the 44 eligible patients was complete response in 6 (13.6%) patients; partial response in 16 (36.4%); stable disease in 18 (40.9%), and progressive disease in 3 (6.8%). In one patient (2.3%), response was not assessable. Objective response after 3 years could be evaluated for 31 patients. The response rate improved for three out these: partial response (PR) => complete response (CR) 1 patient, stable disease (SD) => CR 1 patient, and SD =>PR 1 patient.

Lymphedema as late toxic effect was reported in 10 patients (see Table 2). This edema was grade 1 in five patients; in the

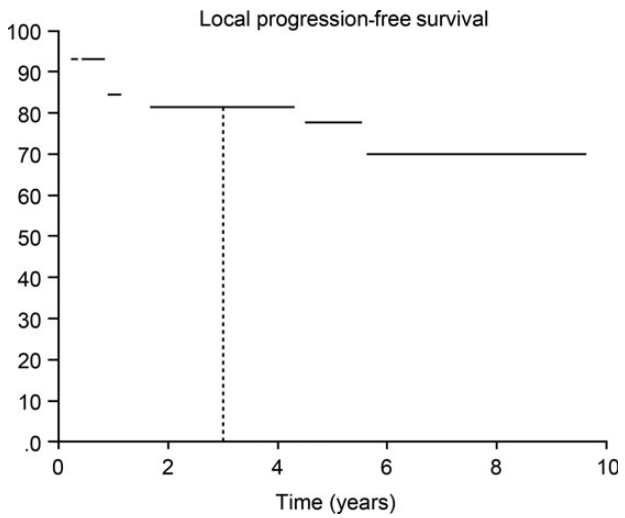

Figure 1. Local progression-free survival. The 3-year local progression-free survival rate was 81.5% (90% one-sided confidence interval 74% to 100%).

Table 2. Late toxic effects according to the RTOG-EORTC scale

	# of patients	Grading[a]
Skin	18	(Grade 3:1 pat., Grade 4: 1 pat.)
Lymphedema	10	(Grade 1: 5 pts., NA: 5 pts.)
Pain	8 (18.2%)	NA
Joint stiffness	2 (4.5%)	NA
Loss of function	2 (4.5%)	NA
Atrophy	1 (2.3%)	NA
Induration/fibrosis	3 (6.8%)	NA

[a]NA = grading not indicated.

other five patients, the lymphedema was not graded. Other late adverse effects were skin toxic effects in 18 patients (2 with grade 3–4) and pain events in 8. Less often, fibrosis (three patients), atrophy (one patient), joint stiffness (two patients), and loss of function (two patients) were seen. During the follow-up period, no secondary tumors were observed.

discussion

The findings from this multicenter phase II study show that moderate dose radiotherapy is an effective treatment option for patients with inoperable progressive DF. This is the first prospective study for a local treatment modality in this rare disease.

Treating DF by any modality should be based on an individualized decision-making process. The natural course of disease is uncertain and varies greatly between individuals. Spontaneous regression and long periods of growth arrest together with the potential harmful effects of therapeutic interventions are arguments for a restrained treatment strategy such as a wait-and-watch policy [6]. Classically, surgery has been the therapeutic mainstay but patients in this study were considered inoperable by experienced sarcoma surgeons of the study center due to surgery being considered as too mutilating.

In an attempt to provide an adequate dose to obtain local disease control while avoiding the risks of functional impairment or other disadvantages of radiotherapy, a fractionation scheme of 56 Gy in 28 fractions was chosen for this trial based on a critical review of the published literature. At the time of design of the study, we found support for this dose level in the report from the MD Anderson series that showed no dose response above this dose [15].

The result of this study demonstrates that this goal was achieved in the majority of patients with 81.5% absence of local progression at 3 years after registration. Adding these results to the growing number of already published experiences of several institutions provides solid evidence for the value of radiotherapy for inoperable progressive DF [8, 9, 16]. A remarkable observation from these studies is that radiotherapy as a single modality seems at least as effective in terms of reaching local disease control as in case of radiotherapy after surgery with positive resection margins.

The results of the present study show that in large lesions, where R0 resection is not likely achievable and therefore postoperative radiotherapy has to be anticipated, or when the planned resection is judged to be associated with considerable morbidity, one should consider radiotherapy as single modality in the primary setting and in case of relapse after prior surgery.

It is important to realize that patients who benefit from radiotherapy do so by having no progression for an extended time interval although not routinely achieving a radiological complete response. Slow but continuous regression of the mass over years with often a residual lesion that remains stable is frequently seen. In this study only six (13.6%) complete responses were seen during the first 3 years after start of treatment.

Treatment associated late toxic effect is hard to evaluate due to the very large lesions that often lead to mass-associated symptoms and discomfort. Nerve compression, edema, and pain are common signs of high growth rate. While successful radiotherapy often leads to growth arrest, tumor shrinkage, and symptomatic relief, one can also observe permanent morbidity by the long disease history and locally aggressive growth pattern combined with treatment-related side-effects. In this multicenter study, no comparison of pre- and post-treatment symptoms and functional level was carried out. The reported toxic effect in the evaluation forms were as expected for this treatment approach such as pain, muscle and joint stiffness, and limb edema. The median follow-up is too short to evaluate correctly radiation-induced sarcoma. In extremity or trunk soft tissue sarcoma, treatment similar to radiotherapy techniques are used, and from this experience, 56 Gy is generally considered as an acceptable dose with an associated low risk of grade 3 or 4 late morbidity. However, late effects of radiotherapy in the relatively young population of fibromatosis patients deserve more attention. Given the rarity of the disease, we plea for an international registry to get a better insight into this subject. Many questions remain unanswered in this study. For statistical reasons, we were not able to identify predictive factors for progression or tumor response. We can also not confirm whether the chosen radiotherapy dose level was optimal. We therefore strongly recommend centralization of treatment in this rare disease given the unpredictable clinical behavior and the difficult management decisions. However, the study was able to demonstrate that radiotherapy at a dose level of 56 Gy is an effective treatment option for progressive DF in patients for whom surgery is unattractive and for whom radiotherapy can be applied without serious morbidity.

acknowledgements

Contribution of patients and investigators who participated in these studies is gratefully acknowledged.

funding

This publication was supported by Fonds Cancer (FOCA) from Belgium.

disclosure

The authors have declared no conflicts of interest.

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Annals of Oncology 24: 2676–2680, 2013
doi:10.1093/annonc/mdt252
Published online 12 July 2013

Limb preservation surgery with extracorporeal irradiation in the management of malignant bone tumor: the oncological outcomes of 101 patients

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Received 7 April 2013; revised 1 June 2013; accepted 3 June 2013

Background: En bloc resection, extracorporeal irradiation (ECI) and reimplantation have been used selectively at our centers as part of limb preservation surgery of malignant bone tumors since 1996. We report the long-term oncological outcomes.

Patients and methods: One hundred one patients were treated with ECI at two Australian centers between 1996 and 2011. A single dose of 50 Gy was delivered to the resected bone segments. The irradiated bones were reimplanted immediately as a biological graft. Patients were treated with chemotherapy as per standard protocol. The three main histological diagnoses were Ewing's sarcoma (35), osteosarcoma (37) and chondrosarcoma (20). There were nine patients with a range of different histologies.

Results: There was one local recurrence (2.86%) in Ewing's sarcoma and the 5-year cumulative overall survival was 81.9%. There was no local recurrence in osteosarcoma and five distant recurrences. The 5-year cumulative overall survival was 85.7%. The local recurrence rate was 20% (4 of 20) in chondrosarcoma, and the 5-year cumulative overall

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