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Intraoperative Radiotherapy and External Beam Radiotherapy in the Multidisciplinary Management of Desmoid Tumors

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Abbreviations: IORT: Intraoperative Radiotherapy; EBRT: External Beam Radiotherapy; PTV: Planning Target Volume; DFS: Disease Free Survival; LFS: Local Free Survival; DMFS: Distant Metastases Free Survival; OS: Overall Survival

Introduction

Desmoid tumors or aggressive fibromatosis are benign neoplasms of connective tissue. These tumors are rare and represent less than 0,03% of all neoplasms [1]. The annual incidence in adults in Europe are around 2-3 cases per million per year. Around 10-15% [2] patients with polyposis adenomatous familiar develop desmoids tumors. Desmoid tumors are fibroblastic lesions with aggressive, infiltrate and destructive growth which frequently recurrent if not widely resected. There are three major anatomic locations: extra-abdominal, intra-abdominal and extremities. The optimal management of desmoid tumors is still controversial. It requires a multidisciplinary approach. High-risk tumors of local recurrence should be managed to decrease the risk, maintaining maximal function in organ affected. Radiotherapy allows decrease local recurrence, however it has not demonstrated improve overall survival. A multicenter study [3], concluded that radiotherapy was associated with improve local control in postoperative patients as well as in primary treatment of unresectable.

In our institution, routine clinical practice is complete surgery with intraoperative radiotherapy (IORT) followed external beam radiotherapy (EBRT). All cases are assessed in a multidisciplinary committee. The aim of the present study is to review our experience using IORT with EBRT in the multidisciplinary management of desmoids tumors.

Table 1: Patients characteristics, NED: Not Evidence of Disease.

Patient No	Gender/ Age	Presentation	Location	Sugical Resection	IORT	Adjuvant treatment	Local relapse	Distant relapse	Outcome on last follow-up
1	M/20	Primary	extra-abdominal	Yes	18Gy	EBRT 46 Gy	no	no	NED
2	M/30	Primary	extra-abdominal	Yes	-	EBRT 60 Gy	yes	no	NED
3	M/17	Primary	lower extremity	Yes	14Gy	EBRT 46 Gy	no	no	NED
4	F/65	Primary	extra-abdominal	Yes	16Gy	EBRT 44 Gy	no	no	NED
5	M/53	Primary	extra-abdominal	Yes	14Gy	EBRT 46 Gy	no	no	NED
6	F/30	Primary	intra-abdominal	Yes	15Gy	EBRT 66 Gy	yes	no	NED
7	F/62	Primary	lower extremity	Yes	-	EBRT 46 Gy	yes	yes	Death
8	M/39	Primary	lower extremity	Yes	-	EBRT 64 Gy	no	no	NED

Material and Methods

Patients

From January 2000 to December 2014, 8 consecutive patients with pathologically confirmed desmoid tumors were prospectively entered into a data registry. All patients signed an informed consent before data registration. Patients were followed and reviewed by both radiation oncologists and orthopedics or general surgeons to evaluate patterns of local and distant failures, acute and long-term toxicity and survival.

Patients' registry included 3 females and 5 males with a median age of 39 years (range 17-65 years). Desmoids tumors were located in the extremities in 5 patients (62,5%), cervical in 1 patient (12,5%) and abdominal location in 2 patients (22,2%). Mean tumor size was 5,6 (1,3-13,5 cm). One of the tumors was >10cm at the largest point. Three patients (37,5%) were referred with recurrent tumor after previous surgery, two patients were referred to us after previous two surgeries and one patient was referred to us after previous three surgeries. Among 8 patients, 5 patients underwent marginal resection, 2 patients had wide local excision and 1 patient had only biopsy. Resection margin was positive in 5 patients (62,5%). Complete patients characteristics are detailed in Table 1.

Treatment course

Surgical procedure at the time of IORT was considered as wide excision (margins >1 cm) and as marginal resection. IORT was considered in 2 patients in the first time and in local recurrence in the 3 patients more. After surgical resection of the desmoid tumor in 5 patients (62,5%), a cylindrical lucite applicator of appropriate diameter was selected and positioned by the radiation oncologist and the surgeon to encompass the surgical bed at high risk of harboring microscopic tumor cells with 1-2 cm of margin around. Before the administration of IORT maximal efforts were made to mobilize uninvolved organs, nerves and vessels out of the treatment field. Occasionally, lead shielding was positioned to assure normal tissue tolerance. When necessary, a bolus was used to homogenize the surface of IORT field. Radiotherapy was administered by using a linear accelerator (Elekta Precise, Elekta AB, Stockholm, Sweden) situated in close proximity to the operating theatre. Median IORT dose was 15 Gy (range 14-18 Gy) with electron beam energies of 4-18 MeV.

6 patients received postoperative EBRT. EBRT was applied with a linear accelerator providing 6 and 15 MV photons with 3D conformal treatment planning. Planning target volume (PTV) was designed to cover the surgical tumor bed with an adequate margin avoiding dose delivery to the entire limb and underlying bone circumferences or joints in order to minimize late adverse squeals. Whenever possible, all surgical scars were included in the irradiation volume. Median dose administered with EBRT in patients after IORT and surgery was 46,4 Gy (range 44 to 50 Gy) with standard fractionation of 1.8-2 Gy/day, 5 days/week over 4.8 to 5.5 weeks, and patients who not received IORT were 63.3Gy (60-66Gy) with standard fractionation of 1.8-2Gy/day, 5 days/week over 6.6 to 7.3 weeks.

The rationale for intraoperative radiotherapy (IORT) lies on the possibility of applying a single high radiation dose to the surgical bed that allows sterilization of microscopic diseases while sparing surrounding organs at risk by mobilizing or shielding the normal tissues presented into the radiation field. The existing evidence based upon randomized studies suggests that IORT combined with EBRT could improve local control in desmoids tumors. All patients were followed-up regularly with a physical examination every 3-6 months for 5 years and yearly thereafter. Computed tomography or magnetic resonance imaging of the involved region was repeated every 3-6 months for 2-3 years, then every 6 months up to 5 years and annually thereafter. Local failure was confirmed by a biopsy. Recurrent disease was defined as in field or out of field.

Statistical analysis was performed using the SPSS software program (Version 22.0, IBM). Disease free survival (DFS) was estimated from the last day of EBRT or the day of surgery and IORT until locoregional or distant relapse. Local free survival (LFS) and distant metastases free survival (DMFS) were estimated at the time of first event. Patients dying from inter-current disease without evidence of tumor were censored at the date of death. Overall survival (OS) was defined as the time interval between treatment and the date of death, whatever the cause, or to the date of last follow-up. Actuarial LFS, DMFS, DFS and OS were calculated using the Kaplan-Meier method. Univariate analysis on loco regional control was evaluated by using the log-rank test. A level of $p<0,05$ was considered statistically significant. No multivariate analysis was performed because of the small sample size of this study. Acute and late complications were scored according to the CTCAE v3.0 scale proposed by the National Cancer Institute. The toxicities reported included only those attributable to local treatments applied. Toxicities related to chemotherapy or other systemic treatments are not included. National rules do not require ethical committee approval by the retrospective study.

Results

The median follow-up of all patients was 54 months (3-135 months). At time of analysis, 7 (87.5%) patients remain alive without evidence of local or distant recurrence and one (12.5%) patient had died because of tumor progression. 3 patients operated without radiotherapy, relapsed and after received this treatment. One patient relapsed after EBRT and died by progression. Time to local recurrence was one month. The overall survival and disease-free-survival rate at 2 years was 87,5%.

Acute and late toxicity

Acute toxicities due to EBRT consisted of epithelitis and diarrhea grade 2 in two patients. No late toxicity had been

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observed during the follow-up period. All parameters were analyzed with regard to age at diagnoses above or below 50 years, sex, primary location, tumor size, and status of resection margins, delaying time between IORT and EBRT and the dose of both IORT and EBRT. No factors were found with either local or distant relapse free survival or overall survival. The limited number and the great heterogeneity of our group of patients probably contributed to the impossibility of identifying statistically significant prognostic factors.

Discussion

The management of desmoid tumors is controversy. Local recurrence is around 20-90% [3,4]. The complete surgical excision was related with increase of local control in several studies [5,6]. But, Reitamo et al. [7] reported that after surgery, the frequency of recurrence was not statistically different, regardless of whether the tumor was completely removed or not. Radiotherapy is a good option to adjuvant treatment. Randomized studies demonstrate effectiveness of adjuvant radiotherapy. Functional results after limb-sparing treatment of desmoid tumors are highly influenced by surgery and radiotherapy doses.

The local control in the literature is varied [3,8-10]. A review demonstrated [3] an increase in rates of local control with either surgery with radiotherapy or radiotherapy alone than surgery alone regardless of the margins achieved at surgery. Doses of radiotherapy are not standard.

Micke et al. [8] reported 81,4% local control with EBRT median dose of 60Gy. Roeder et al. [11] used IORT with a median dose of 12Gy combined with EBRT median dose 45Gy, with 3-year local control rates of 82% overall and 91% inside the IORT areas, similar to us. These studies are difficult to compare due to heterogeneity. Postoperative EBRT doses between 50-65 Gy results in adequate local control rate [10]. Guadagnolo et al. [12], demonstrated that postoperative doses more than 56 Gy were associated with late moderate to severe complications in terms of soft tissue necrosis, fibroses, edema, fracture, vascular complications requiring limb amputation, neuropathy, osteoarthritis and enteritis without increase of local control. In this study two factors more associated complications, age and radiotherapy without surgery. Ballo et al. [4], concluded that local recurrence rates do not appear to be reduced by the use of higher doses.

Nuyttens et al. [3] reported complications in radiotherapy treatment, included edema, cellulitis, paresis, fibroses, ulcers, fractures, and second malignancy. Fibrosis was the most common complication. Paresis was often caused when the tumor was adherent to the nerve. Cellulitis was predominantly seen in obese female patients. When bone was irradiated increased pathologic fractures. Only 2 patients with second malignances were described in this serie. Kriz et al. [10] described 40% skin reactions grade 2. Our acute toxicity was minor and due to EBRT, only 2 patients developed diarrhea and ephitelitis grade 2 and not late toxicities were observed, but we think that late effects are difficult to analyze as long term complications can be originated by the multiple treatment modalities implicated even more in a group of patients in which a multidisciplinary approach is very often required. No cases of severe fibrosis, chronic mild lymphedema, fractures and other toxicities have been observed on follow-up. Severe radiogenic side effects as well as secondary malignances were not observed in this collective. With the proper caution concerning the relatively short follow-up of our series, we believe that our results compares well with data observed from other different groups with similar patients that included local IORT as a component of the treatment.

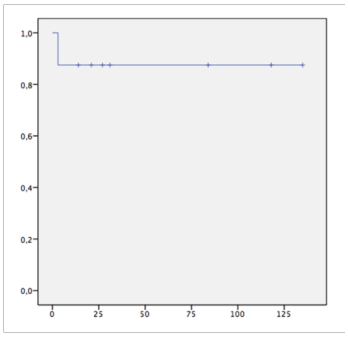

Figure 1: Kaplan-Meier survival analysis showing the calculated probability of overall survival.

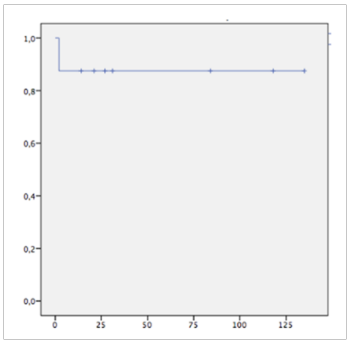

Figure 2: Kaplan-Meier survival analysis showing the calculated probability of disease-free survival.

The efficacy of postoperative EBRT is limited due to the inability to deliver adequate doses of irradiation on account of the dose tolerance limits of small bowel, spinal cord, stomach, kidney and liver. IORT is a possibility to overcome these limitations and to escalate the dose specialty in intra-abdominal, pelvis and mesenteric desmoids. IORT can be delivered alone or with additional EBRT before o after surgery. However, IORT is preferred as a boost dose in combination with EBRT and maximal surgical resection because of the potencial advantages associated with this approach [11]. Further advantages are the decreasing of the dose of postoperative EBRT necessary to obtain an adequate local control, with the possibility of decreasing late complication, and the avoiding of tumoral repopulation during the surgery to radiotherapy interval. Finally, IORT permits to shorten the overall radiation treatment time by delivering the

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boost dose to the tumor bed immediately after surgical resection. We report the results of our analysis of a series of patients with desmoid tumors treated in our Radiation Oncology department. We recognize the limitations of our study, in particular the small number of cases, heterogeneity or short follow up. We consider IORT a good option to deliver high dose without increase toxicities (Figures 1 & 2).

Conclusion

In conclusion, IORT is an attractive boosting procedure to be considered in the radical management of desmoid tumors. This technique should permit a decreasing of the postoperative required radiation dose without compromising final outcome and could improve local control in selected cases. Based upon the evidence existing in the literature and our own data of feasibility and clinical outcomes, and although follow-up is still not long enough to make a definitive statement on late toxicities, it is now our institution policy to consider IORT as a boost to EBRT for all patients with desmoid tumors as well as tumors of extremities in whom proximity to critical structures preclude a limb preservation approach.

References

1. Bonvalot S, Desai A, Coppola S, Le Péchoux C, Terrier P, et al. (2012) The treatment of desmoid tumors: a stepwise clinical approach. Ann Oncol 23(10): 158-166.
2. Shin KH, Shin SJ, Lee DH, Kang ES, Suh CO (1999) The Role of Radiotherapy in the Treatment of Aggressive Fibromatosis. Yonsei Med J 40(5): 439-443.
3. Nuyttens JJ, Rust PF, Thomas CR, Turrisi AT (2000) Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: a comparative review of 22 articles. Cancer 88(7): 1517-1523.
4. Ballo MT, Zagars GK, Pollack A, Pisters PW, Pollack RA (1999) Desmoid tumor: prognostic factors and outcome after surgery and radiation therapy. J Clin Oncol 17(1): 158-167.
5. Merchant NB, Lewis JJ, Woodruff J, Leung DH, Brennan MF (1999) Extremity and trunk desmoid tumors: a multifactorial analysis of outcome. Cancer 86(10): 2045-2052.
6. Leithner A, Gapp M, Leithner K, Radl R, Krippl P, et al. (2004) Margins in extra-abdominal desmoid tumors: a comparative analysis. J Surg Oncol 86(3): 152-156.
7. Reitamo JJ, Scheinin TM, Hayry P (1986) The desmoid syndrome. New aspects in the cause, pathogenesis and treatment of the desmoid tumor. Am J Surg 151(2): 230-237.
8. Micke O, Seegenschmiedt M (2005) Radiation therapy for aggressive fibromatosis (desmoid tumours): results of a national Patterns of Care Study. Int J Radiat Oncol Biol Phys 61(3): 882-891.
9. Baumert BG, O Spahr M, Von Hochstetter, Beauvois S, Landmann C, et al. (2007) The impact of radiotherapy in the treatment of desmoid tumours.An international survey of 110 patients. A study of the Rare Cancer Network. Radiat Oncol 2: 12
10. Kriz J, Eich HT, Haverkamp U, Seegenschmiedt MH, Heide J, et al. (2014) Radiotherapy is effective for desmoid tumors (aggressive fibromatosis)-Long-term results of a German Multicenter study. Oncol Res Treat 37(5): 255-260.
11. Roeder F, Timke C, Oertel S, Hensley FW, Bischof M, et al. (2010) Intraoperative electron radiotherapy for the management of aggressive fibromatosis. IntJ Radiat Oncol Biol Phys 76(4): 1154-1160.
12. Guadagnolo BA, Zagars GK, Ballo MT (2008) Long-term outcomes for desmoid tumors treated with radiation therapy. Int J Radiat Oncol Biol Phys 71(2): 441-447.

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