The place of radiotherapy in the management of desmoid tumors

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ABSTRACT

The management of desmoid tumors has undergone changes in recent years including active surveillance for asymptomatic and non-progressive tumors. The place of radiotherapy is contested due to significant toxicity. Radiation therapy is offered as an alternative to surgery for tumors that are unresectable or whose removal exposes functional or life damage.

In view of the high recurrence potential, radiotherapy should also be discussed after surgery for desmoid tumors. Irradiation has shown its benefit in terms of local control for tumors whose excision is incomplete. Its place after full surgery is controversial.

Through this review of the literature, we propose to support the indications for radiotherapy in the management of desmoid tumors and to present its technical aspects.

*Keywords: [*desmoid, *tumor, treatment]*

1. INTRODUCTION

Desmoid tumors are monoclonal proliferations of fibroblasts and myofibroblasts belonging to soft tissue tumors. They are rare and originate from mesenchymal stem cells. They can be sporadic or hereditary (1).

Their etiopathogenesis remains poorly understood, involving a traumatic cause and genetic and hormonal factors (2, 3). The β catenin is considered a diagnostic, prognostic and therapeutic biomarker (3). Desmoid tumors are distributed according to site into intra-abdominal and extra-abdominal tumors including tumors of the abdominal wall (2,4). , considered benign, do not give secondary locations but have a significant local and locoregional destructive power associated with a significant risk of local relapse after treatment.

Their evolution is unpredictable with phases of stabilization, regression and scalability. As a result, the management of these tumors remains non-standardized (2).

Locoregional treatment should be considered for progressive tumors. Surgery was for a long time the first-line treatment for resectable tumors.

Treatment strategies have recently changed with the adoption of a new attitude of active surveillance recommended for non-progressive tumors in asymptomatic patients (4).

Radiotherapy appears to provide a benefit for unresectable tumors or insufficient excision. Its place is controversial given the lack of a high level of scientific evidence and significant toxicity.

In this review of the literature, we are interested in supporting the indications for radiotherapy in the management of desmoid tumors of the abdominal and extra-abdominal wall.

2- PLACE OF EXCLUSIVE RADIOTHERAPY

In the majority of teams, the therapeutic sequence of desmoid tumors went through surgical excision. Surgery with healthy margins is the treatment of choice, offering a 5-year local control rate ranging from 72% to 78% depending on the series (4- 6) (table 1).

Due to extensive tumor extension, macroscopically complete surgery is often either impossible or unacceptable, exposing major functional complications or cosmetic damage (7). R0 excision was only possible in 58% of patients in the metanalysis published by Janssen et al in 2017 on 1005 patients. (4) The sequelae of surgery should be considered in young patients of median age varying between 28 and 35 years (5 , 8).

In fact, complications such as amputations and disability are reported in 4% of operated patients (6).

Exclusive radiotherapy has emerged as an alternative to surgery, but its place remains poorly established given the lack of randomized trials comparing the two treatment modalities.

An early study published in 1993, involving 40 patients, reported a risk of progression after surgery of 29%. This rate was higher compared to that after radiotherapy, estimated at 19% (9).

Keus et al, in a prospective phase II study of the EORTC concerning 44 patients, showed a local control rate at 3 years of 81.5% after exclusive radiotherapy with stabilization of the disease in 41% of cases and a response complete in 13.6% of patients (10).

A comparative review of 22 articles, grouping together 780 patients and excluding abdominal and head and neck tumors, reported local control rates at 3 years by radiotherapy alone of 83 and 73% respectively for primary and recurrent tumors versus 78% and 79 % by a combination of surgery and radiotherapy (6).

The local control rate at 4 years was 78% in a recently published retrospective study involving 50 patients, half of whom received radiotherapy alone. This rate was comparable to surgical results (5).

Bishop et al, in a series of 209 patients treated with radiotherapy alone, reported local control rates at 5 years and 10 years of 64 and 61%, respectively, which were significantly lower compared to combined treatment. In multivariate analysis, an age less than 30 years and a tumor size greater than 10 cm are associated with a greater risk of relapse.

Patients under 30 years of age had a local control rate at 3 years of 43% compared to 75% for patients over 30 years (11). This finding was also reported in other series with cut-off ages varying between 20 and 40 years. The authors suggested the hypothesis of an intricate radioresistance to a genetic predisposition in young patients (11, 12, 13, 14, 15).

The role of exclusive radiotherapy for recurrent tumors was also studied by Nuyttens et al (6) who reported a local control rate at 3 years of 73% for recurrences treated with exclusive radiotherapy. This rate was higher compared to treatment of relapses by surgery alone.

Although there is no direct comparison between the two treatment modalities, the local control rates reported in the series of exclusive radiotherapy were not inferior to the results of the surgical series (11, 12). Many authors recommend radiotherapy as an alternative to surgical treatment for locally advanced tumors whose removal would be responsible for significant damage (5, 11, 13, 14, 16 - 17).

3- PLACE OF ADJUVANT RADIOTHERAPY

Combined treatment with surgery and radiotherapy was the most common treatment approach to resectable desmoid tumors.
According to the review by Nuyttens et al of 780 patients, excluding abdominal, head and neck locations, this combination offers a better rate of local control at 3 years in the event of R1 excision compared to surgery alone. This rate increases from 41% to 75% in the case of combined treatment (p = 4.10-10) (table2).
In fact, the authors reported a significant gain in local control at 3 years by the combination of radiosurgery versus exclusive surgery, even in the event of complete R0 type excision (94% versus 72% with p = 0.0048). This gain was found for both primary and recurrent tumors (6) (table 3).
These results were also supported by the review published by Janssen et al in 2017 about 1295 patients of which 1005 had surgery alone and 290 patients had adjuvant radiotherapy. The combined treatment was superior to excision alone with a statistically significant difference in terms of local control.
This gain was significant for both primary tumors and recurrent tumors in the event of insufficient excision. In contrast, surgery alone was better than a combination of radiotherapy with full R0 surgery (4) (table 4).
However, excess with positive margins was not associated with an increased risk of recurrence in a surgical series by Lev et al in 189 patients treated with surgery and / or radiotherapy (18). Some authors recommend close monitoring in the event of incomplete resection without recourse to adjuvant radiotherapy, which will only be initiated in the event of symptomatic progression and after discussion in a multidisciplinary team (5,7,16, 17)

4- TECHNICAL ASPECTS OF RADIOTHERAPY

The dose prescribed in the different studies varied between 30 and 75 Gy. A comparison of local relapse rates according to dose levels showed that a dose above 50 Gy significantly improves local control (6).
On the other hand, a dose escalation beyond 56Gy was associated with a significant increase in toxicity in a study involving 115 patients treated with exclusive or adjuvant radiotherapy (11).
Irradiation according to IMRT and VMAT techniques has been compared to 3D irradiation in patients treated for desmoid tumors of the chest wall. New techniques offer better dose distribution with reduced dose to healthy organs (19).
CTV should encompass the surgical bed in case of adjuvant radiotherapy. When radiotherapy is the primary treatment, GTV should include all the tumor. Margins are added to GTV to obtain CTV.

5- THE TOXICITY OF RADIOTHERAPY

The evaluation of the results of radiotherapy necessarily involves an evaluation of post-radiation toxicity. Late toxicity such as edema, paresthesia, stiffness and weakness is described in 36% of the cases of the radiotherapy series against 20% in the surgical series (20).
Skin toxicity was the most represented in the different series. It was like lymphedema in 20% of cases and fibrosis in 6 to 9% of cases (6, 10).
Radiation-induced cancers were reported in 0.7% of patients in the metanalysis published in 2000 about 780 patients and in 2% of cases in a series of 115 patients, 34 of whom received a dose greater than 56 Gy (6 and 13). Di Marco et al report a case of radiation-induced pleomorphic cell sarcoma 21 years after re-irradiation of a recurrent desmoid tumor in the pelvic region (21).

7- CONCLUSION

Although the rates of local control after radiotherapy for desmoid tumors are satisfactory, the place of irradiation alone or in combination with surgery remains controversial. It is recommended for advanced tumors where excision is impossible or decaying. Its place after surgery is questionable given its non-trivial toxicity.
Despite the rarity of this entity, it is imperative to optimize its management through randomized trials comparing the different treatment modalities.

COMPETING INTERESTS

Conflict of interest:None

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript."

Table 1: Results of exclusive radiotherapy

	Number	Median follow-up	Mean Dose of radiotherapy	Results
J C Acker and al (9)	40	57.5	54	19% Progression after radiotherapy Vs 29% after surgery
Keus and al (10)	44	57.6	54	- Local control rate at 3 years 81.5 - Stabilization of the disease: 41% - A complete answer: 13.6%
J J Nuyttens and al (6)	780	56.2	52.8	Local control rate at 3 years: - Abdominal tumors 83% - Head and neck tumors 73%
A M Hong and al(5)	50	51	50.4	Local control rate at 4 years: 78%
Bishop and al(11)	209	98	50.6	Local control rate : - at 5 years 64% - at 10 years 61%

Table 2: Local control for free margin and positive margin treated with surgery alone or surgery with radiotherapy

	Surgery alone	Surgery + Radiotherapy	
	%	%	***P*** value

Free margin	72	94	0.0048
Positive margins	41	75	$4*10^{-10}$
Total	61	75	0.0002

P value in comparison with surgery alone.

Table 3: Local Control after Treatment of Primary, Recurrent tumor

	Surgery alone	**Surgery + Radiotherapy**	
	%	%	***P*** value
Primary tumor	62	78	0.027
Recurrence	47	79	$2*10^{-5}$

P value in comparison with surgery alone.

Table 4 : Summary of treatment outcomes for surgery and surgery with adjuvant radiotherapy according to surgical margin according to the Janssen study

		Recurrence rate	
Margin	**Referral status**	**Surgery**	**Surgery+radiotherapy**
R0	Primary Recurrent	15.2 % 36 %	22 % 29 %
R1	Primary Recurrent	29 % 73 %	23.8 % 38 %
R2	Primary Recurrent	64 % 100 %	21 % 56 %
Total	Primary Recurrent	25.6 % 52.7 %	22.7 % 36 %

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