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2 **The place of radiotherapy in the management of**
3 **desmoid tumors**

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14 **ABSTRACT**
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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.

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17 *Keywords: [desmoid, tumor, treatment]*
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20 **1. INTRODUCTION**
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22 Desmoid tumors are monoclonal proliferations of fibroblasts and myofibroblasts belonging to
23 soft tissue tumors. They are rare and originate from mesenchymal stem cells. They can be
24 sporadic or hereditary (1).

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

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

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

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

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

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

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44 2- PLACE OF EXCLUSIVE RADIOTHERAPY

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

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

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

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

59 An early study published in 1993, involving 40 patients, reported a risk of progression after
60 surgery of 29%. This rate was higher compared to that after radiotherapy, estimated at 19%
61 (9).

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

65 A comparative review of 22 articles, grouping together 780 patients and excluding abdominal
66 and head and neck tumors, reported local control rates at 3 years by radiotherapy alone of
67 83 and 73% respectively for primary and recurrent tumors versus 78% and 79 % by a
68 combination of surgery and radiotherapy (6).

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

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

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

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

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

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89 3- PLACE OF ADJUVANT RADIOTHERAPY

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90 Combined treatment with surgery and radiotherapy was the most common treatment
91 approach to resectable desmoid tumors.
92 According to the review by Nuyttens et al of 780 patients, excluding abdominal, head and
93 neck locations, this combination offers a better rate of local control at 3 years in the event of
94 R1 excision compared to surgery alone. This rate increases from 41% to 75% in the case of
95 combined treatment ($p = 4.10 \cdot 10^{-10}$) (table2).
96 In fact, the authors reported a significant gain in local control at 3 years by the combination
97 of radiosurgery versus exclusive surgery, even in the event of complete R0 type excision
98 (94% versus 72% with $p = 0.0048$). This gain was found for both primary and recurrent
99 tumors (6) (table 3).
100 These results were also supported by the review published by Janssen et al in 2017 about
101 1295 patients of which 1005 had surgery alone and 290 patients had adjuvant radiotherapy.
102 The combined treatment was superior to excision alone with a statistically significant
103 difference in terms of local control.
104 This gain was significant for both primary tumors and recurrent tumors in the event of
105 insufficient excision. In contrast, surgery alone was better than a combination of radiotherapy
106 with full R0 surgery (4) (table 4).
107 However, excess with positive margins was not associated with an increased risk of
108 recurrence in a surgical series by Lev et al in 189 patients treated with surgery and / or
109 radiotherapy (18). Some authors recommend close monitoring in the event of incomplete
110 resection without recourse to adjuvant radiotherapy, which will only be initiated in the event
111 of symptomatic progression and after discussion in a multidisciplinary team (5,7,16, 17)

112 113 **4- TECHNICAL ASPECTS OF RADIOTHERAPY**

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

127 128 **5- THE TOXICITY OF RADIOTHERAPY**

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130 The evaluation of the results of radiotherapy necessarily involves an evaluation of post-
131 radiation toxicity. Late toxicity such as edema, paresthesia, stiffness and weakness is
132 described in 36% of the cases of the radiotherapy series against 20% in the surgical series
133 (20).
134 Skin toxicity was the most represented in the different series. It was like lymphedema in 20%
135 of cases and fibrosis in 6 to 9% of cases (6, 10).
136 Radiation-induced cancers were reported in 0.7% of patients in the metanalysis published in
137 2000 about 780 patients and in 2% of cases in a series of 115 patients, 34 of whom received
138 a dose greater than 56 Gy (6 and 13). Di Marco et al report a case of radiation-induced
139 pleomorphic cell sarcoma 21 years after re-irradiation of a recurrent desmoid tumor in the
140 pelvic region (21).

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143 **7- CONCLUSION**

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

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151 **COMPETING INTERESTS**

152 Conflict of interest:None

154 **AUTHORS' CONTRIBUTIONS**

155 All authors read and approved the final manuscript."

162 **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%

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

	Surgery alone	Surgery + Radiotherapy	
	%	%	P value

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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

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

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