ANTICANCER RESEARCH *42*: 4485-4492 (2022)
doi:10.21873/anticanres.15949

Intraoperative Brachytherapy Combined With Adjuvant Radiotherapy Shows Equal Results in the Treatment of Leiomyosarcoma on the Extremities Compared to Adjuvant Radiotherapy Only – A Multicentric Retrospective Analysis

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Abstract. *Background/Aim: Leiomyosarcomas account for 2-10% of all extremity soft tissue sarcomas. The role of intraoperative brachytherapy as an additive booster therapy is not clearly defined. This study focused on the additive value of brachytherapy in the treatment of leiomyosarcomas on the extremities. Patients and Methods: This retrospective multicenter study compared treatment outcomes of 94 patients diagnosed with a primary leiomyosarcoma in their extremities. Patients were divided into three groups according to their radiotherapy protocol: a) adjuvant radiotherapy (aRT), b) neoadjuvant radiotherapy (nRT) and c) intraoperative brachytherapy combined with adjuvant radiotherapy (IOBTaRT). These three treatment groups were compared for local control, time to metastasis, and overall survival. Results: Eleven patients were treated with IOBTaRT, 35 patients with aRT, and seven patients with nRT only. The survival time was 157.6 months for patients in the IORTaRT group, and 111.3 months for patients treated with aRT only. The time to local recurrence was 141.5 months for patients treated with IOBTaRT and 106.1 months for patients treated with aRT. The estimated time to metastasis was 34.6 months for patients in the IOBTaRT group and 69.7 months for patients treated with aRT alone. No significant differences were observed between these treatment groups concerning overall survival, local recurrence, or metastasis. Conclusion: Additive brachytherapy did not provide a significant advantage in the treatment of leiomyosarcomas. However, this study was limited by the number of patients per group.*

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Key Words: Leiomyosarcoma, brachytherapy, radiotherapy, soft-tissue sarcoma, extremity, multicentric analysis.

Leiomyosarcomas (LMSs) are rare malignant tumors that originate in soft tissue or bones. This tumor most frequently occurs in the middle aged to older population (50-70 yr.). LMSs of the soft tissue preferably occur in the retroperitoneum and the great blood vessels (*i.e.*, *vena cava*). These tumors can be divided into three groups: uterine, abdominal (retroperitoneum and gastro-intestinal) and non-visceral (somatic) LMSs (1). In the limbs, LMSs account for 2-10% of all soft-tissue tumors. These tumors can also arise from the bone, but this is extremely rare (1-4).

The current golden standard treatment for soft-tissue sarcomas (STSs) and therefore also for LMSs is resection and (neo-) adjuvant radiotherapy and/or chemotherapy (5). A preference towards neoadjuvant therapy has been documented in recent decades (6). The most known advantages of this sequence are the lower dosage and better focusing of the radiotherapeutic field because of the known tumor size (6). Disadvantages include postoperative infection, wound dehiscence and sometimes unclear margins (6). Intraoperative brachytherapy, described as an efficient complementary technique to surgery and adjuvant RT, is not widely used (7, 8). Even though showing favorable results, this time-consuming technique also needs a special infrastructure, which is not present in every sarcoma center.

To date, the role of an intraoperative brachytherapy as an additive booster therapy in the treatment of leiomyosarcomas in the extremities is not clearly defined. This multicentric-retrospective study aimed to examine whether brachytherapy has additive value in the treatment of leiomyosarcomas on the extremities.

Patients and Methods

The study protocol was approved by the local Ethic committees of each contributing study center. Written informed consent was obtained from all subjects before participation. All methods and measurements were carried out in accordance with relevant guidelines and regulations.

Applying a retrospective multi-centric study design, the clinical records of 94 patients who were treated for a high-grade LMS on the extremity at the Department of Orthopaedics and Traumatology at the Medical University of Innsbruck, LUMC Leiden, Institute Jules Bordet, UCL and the Antwerp University Hospital between 2000 and 2016 were reviewed. Treatment outcomes of patients who received intraoperative brachytherapy in combination with adjuvant RT (IOBTaRT) were compared to outcomes of patients treated with adjuvant RT (aRT) alone and patients treated with neoadjuvant RT (nRT) only. The local recurrence rate was evaluated, as well as time to local recurrence, metastasis rate, time to metastasis, overall survival rate, and survival time.

Preoperative staging consisted of local magnetic resonance tomography, computed tomography of the whole trunk (thorax, abdomen, and pelvis), complete blood count, and serum chemistry analysis. Histologic diagnosis was assessed preoperatively by sonographically-guided or CT-guided core needle biopsy. Inclusion criteria consisted of a) surgical removal of soft tissue sarcomas by marginal surgical resection following the definitions by Enneking *et al*. (9), b) age ≥18 years old, c) minimum follow-up of two years, and d) treatment with intraoperative brachytherapy in combination with adjuvant radiotherapy (IOBTaRT), adjuvant RT (aRT) alone or neoadjuvant RT (nRT) only. Neoadjuvant radiotherapy was given with a dosage of 50 Gy (25×2 Gy). Adjuvant RT was around 60 Gy (30×2 Gy). This was scheduled after removal of the stitches or when the wound was dry and healed. The sequence of treatment for the patients in the IOBTaRT group was surgery and IORT followed by aRT. The technique of IOBT applied has already been reported (Figure 1) (10). The dose of the intraoperative brachytherapy generally was 15 Gy. Postoperative adjuvant RT was started 3-4 weeks after tumor resection. External beam radiation was delivered to a total dose of 50 Gy (given as 2 Gy per fraction) in 5 weeks encompassing the surgical bed with a margin of 3-5 cm. Patients suffering from high-grade sarcoma underwent postoperative doxorubicin-based adjuvant chemotherapy. The patients underwent regular follow-up evaluation at the authors' institution every 3 months, consisting of clinical examination, computed tomography of the whole trunk (thorax, abdomen, and pelvis), and magnetic resonance imaging of the part of the body, which had undergone surgery.

Patients who underwent ablative surgery, intralesional resection with gross tumor remnants, as well as patients with superficial low-grade sarcomas were excluded from the study. Forty-one patients did not full-fill the inclusion criteria and were excluded from further investigations. Fifty-three patients were included in our analysis, consisting of 7 patients (13.2%) treated with nRT alone, 35 patients (66.0%) treated with aRT only, and 11 patients (20.8%) treated IOBTaRT. Details are shown in the Flow-Chart diagram (Figure 2).

Statistical analysis. Patient characteristics were descriptively analyzed. Age at surgery is presented as mean with standard error (SE) and tumor size is presented as median with range. Sex, amputation, tumor location, tumor depth, tumor grade and whoops procedures are expressed as proportions. Local recurrence rate, metastasis rate, and overall survival rate are expressed as proportions and compared between treatment groups using the Fisher's exact test. Survival time, time to metastasis and time to local recurrence were estimated using the Kaplan–Meier method and differences between the treatment groups were compared with the log-rank test. Results were considered significant if $p<0.05$. All statistical analyses were performed with SPSS (IBM SPSS statistics for Windows, Inc, version 27.0; IBM Corp, Armonk, NY, USA).

Results

Fifty-three patients were included in the analysis (Figure 2). These patients were subdivided into three groups according to the RT treatment they received: a) intraoperative brachytherapy combined with adjuvant RT (IOBTaRT), b) adjuvant RT (aRT) alone, and c) neoadjuvant RT (nRT) only. Group characteristics concerning sex, age, amputation after local recurrence, tumor location, tumor size, tumor depth, tumor grade and the performance of whoops procedures are summarized in Table I. None of the patients was lost to follow-up.

Brachytherapy combined with adjuvant radiotherapy versus adjuvant radiotherapy. Eleven patients were treated with intraoperative brachytherapy combined with adjuvant RT and 35 patients were treated with adjuvant RT alone. The proportion of patients who presented with local recurrence was not significantly different between both treatment groups ($p=0.220$) (Table II). In addition, no significant differences were observed between these treatment groups concerning metastasis rate ($p=0.302$) and death rate ($p=0.497$) (Table II). The time to local recurrence was 141.5 months for patients treated with IOBTaRT and 106.1 months for patients treated with aRT alone (Figure 3). There was no significant difference in local recurrence between the treatment groups ($p=0.564$). The time to metastasis was 34.6 months for patients treated with IOBTaRT and 69.7 months for patients treated with aRT alone (Figure 4). No significant difference between the treatment groups was observed ($p=0.133$). The survival time was 157.6 months for patients treated with IORTaRT and 111.3 months for patients treated with aRT only (Figure 5). No significant difference in survival time was observed ($p=0.225$).

Brachytherapy combined with adjuvant radiotherapy versus neoadjuvant radiotherapy. None of the seven patients treated with nRT presented with local recurrence during the observed follow-up period (Figure 6). Five out of these eleven patients (71.4%) suffered from metastasis, and two patients (28.6%) died during the postoperative follow-up period. No significant differences were observed between these groups regarding local recurrence rate ($p=0.119$), metastasis rate ($p=1.000$), and death rate ($p=1.000$) (Table III). For patients treated with nRT alone, the time to metastasis was 16.6 months (Figure 7), and survival time is estimated at 43.2 months (Figure 8). No significant differences were observed for time to local recurrence

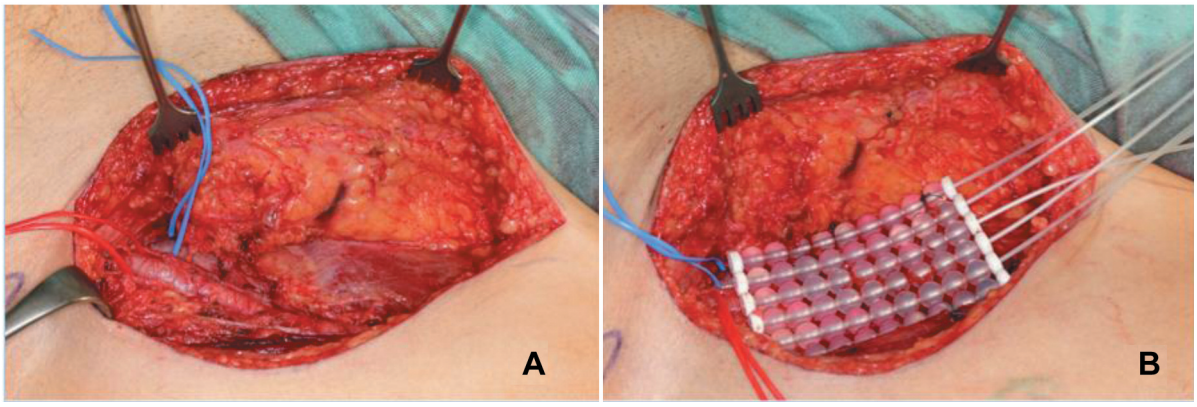

Figure 1. *Tumor bed after wide resection of a leiomyosarcoma around the Arteria femoralis (red vessel loop) and Vena femoralis (blue vessel loop) (A). The correctly placed and fixated flab for the intraoperative brachytherapy (B).*

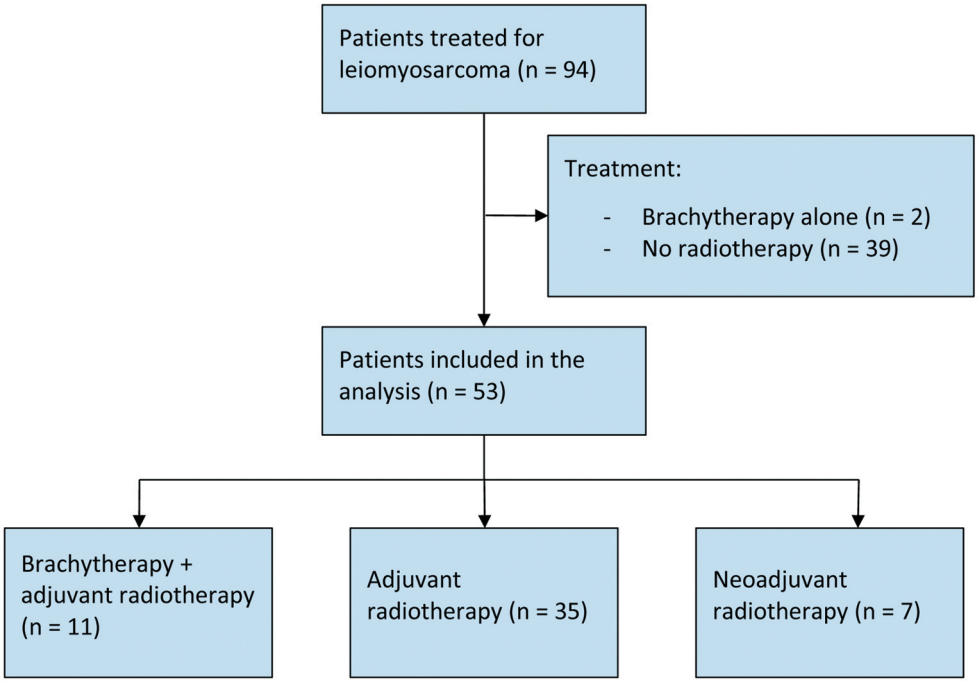

Figure 2. *Patient flow-chart diagram showing the three treatment groups.*

(p=0.225), time to metastasis (p=0.659), and survival time (p=0.388) between patients treated with intraoperative brachytherapy combined with adjuvant RT and patients treated with neoadjuvant RT alone.

Discussion

Leiomyosarcomas are rare tumors, accounting for 10% of soft-tissue sarcomas in the extremities (1). Their treatment remains challenging. The major treatment goal is salvation of the limb with maximal local control and therefore a higher survival rate (11-13). The current golden standard treatment is marginal resection and (neo-) adjuvant RT. Even though time-consuming, brachytherapy in association with adjuvant RT has been reported to obtain more local control with less complications (7, 8, 13, 14). This multicenter study compared the different adjuvant options of RT and their consequences on local control and overall survival.

Table I. *Group characteristics*.

		Brachytherapy + adjuvant RT (n=11)	Adjuvant RT (n=35)	Neoadjuvant RT (n=7)	Total (n=53)
Sex	n (%)				
	Male	6 (54.5%)	20 (57.1%)	6 (85.7%)	32 (60.4%)
	Female	5 (45.5%)	15 (42.9%)	1 (14.3%)	21 (39.6%)
Age (y)	Mean±SE	64±3.8	60±2.3	60±4.2	61±1.8
Amputation	n (%)	1 (9.1%)	4 (11.4%)	0	5 (9.4%)
Tumor location	n (%)				
	Upper leg	11 (100%)	22 (62.9%)	4 (57.1%)	37 (69.8%)
	Lower leg	0	5 (14.3%)	2 (28.6%)	7 (13.2%)
	Upper arm	0	5 (14.3%)	1 (14.3%)	6 (11.3%)
	Lower arm	0	3 (8.6%)	0	3 (5.7%)
Tumor size (mm)	Median (range)	113 (48-228)	22 (2-180)	8 (3-13.6)	48 (2-228)
Tumor depth	n (%)				
	Superficial	2 (18.2%)	7 (20.0%)	4 (57.1%)	13 (24.5%)
	Deep	9 (81.8%)	28 (80.0%)	3 (42.9%)	40 (75.5%)
Tumor grade	n (%)				
	Grade 1	0	1 (2.9%)	0	1 (1.9%)
	Grade 2	3 (27.3%)	9 (25.7%)	3 (42.9%)	15 (28.3%)
	Grade 3	8 (72.7%)	25 (71.4%)	4 (57.1%)	37 (69.8%)
Whoops	n (%)	0	1 (2.9%)	0	1 (1.9%)

Table II. *Local recurrence rate, metastasis rate, and death rate for patients treated with intraoperative brachytherapy and adjuvant radiotherapy, and patients treated with adjuvant radiotherapy alone*.

		Brachytherapy + adjuvant radiotherapy (n=11)	Adjuvant radiotherapy (n=35)	*p*-Value Fisher's exact test
Local recurrence	n (%)	4 (36.4%)	6 (17.1%)	0.220
Metastasis	n (%)	8 (72.7%)	18 (51.4%)	0.302
Death	n (%)	4 (36.4%)	18 (51.4%)	0.497

Table III. *Local recurrence rate, metastasis rate, and death rate for patients treated with intraoperative brachytherapy and adjuvant radiotherapy, and patients treated with neoadjuvant radiotherapy alone*.

		Brachytherapy + adjuvant radiotherapy (n=11)	Neoadjuvant radiotherapy (n=7)	*p*-Value Fisher's exact test
Local recurrence	n (%)	4 (36.4%)	0	0.119
Metastasis	n (%)	8 (72.7%)	5 (71.4%)	1.000
Death	n (%)	4 (36.4%)	2 (28.6%)	1.000

This retrospective analysis did not prove the additive value of brachytherapy in the treatment of STS. No difference in local control, overall survival or time to metastasis was observed between the group treated with brachytherapy and adjuvant RT and the group treated with adjuvant RT alone. For the patient group treated with neoadjuvant RT alone, a very high overall survival and short time to metastasis was noted. No local recurrence was observed in this group of patients. However, the additive value of brachytherapy is described in the literature, certainly in cases with high risk of local recurrence (15). Even though time-consuming, its value has been proven in retroperitoneal (metastatic), colorectal or gynecological tumors. Recent developments make this type of therapy more doable (15, 16).

Brachytherapy is more seen as a booster therapy and less as a monotherapy (15, 17). The place of brachytherapy as monotherapy is only valuable in low-risk situations or in case re-irradiation can be considered afterwards (15). If applied as a booster to adjuvant RT, brachytherapy is described to give excellent local control and limited toxic complications (18). However toxic side effects have been described (13, 15).

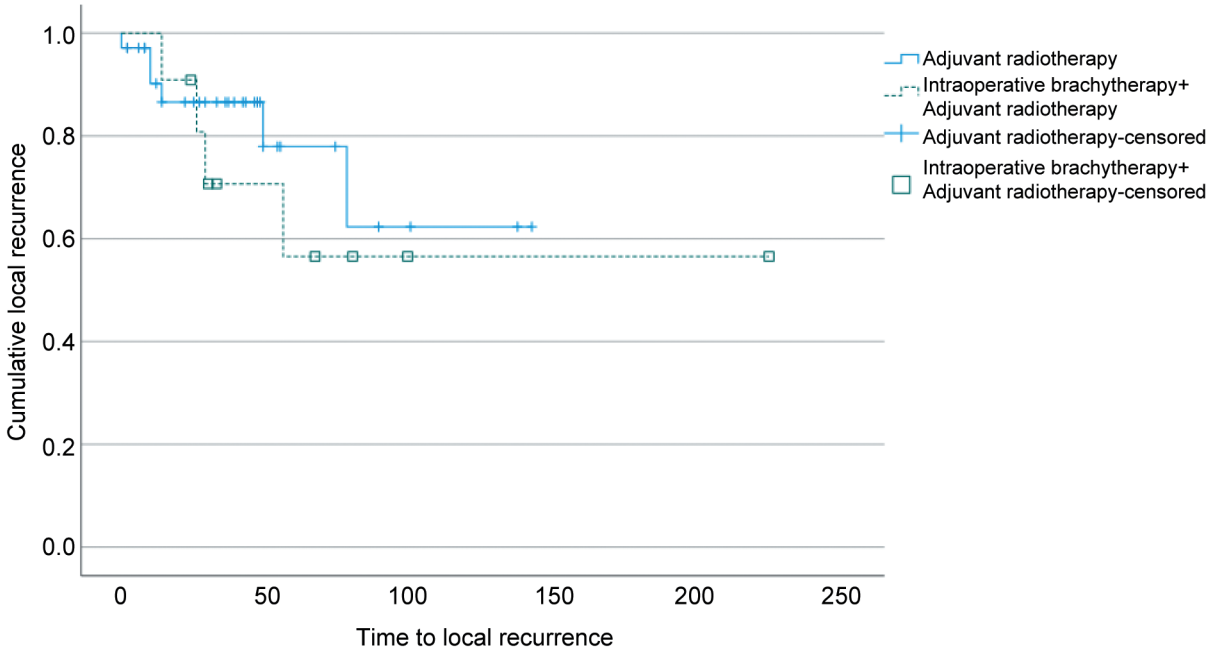

Figure 3. *Time to local recurrence for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with adjuvant radiotherapy alone.*

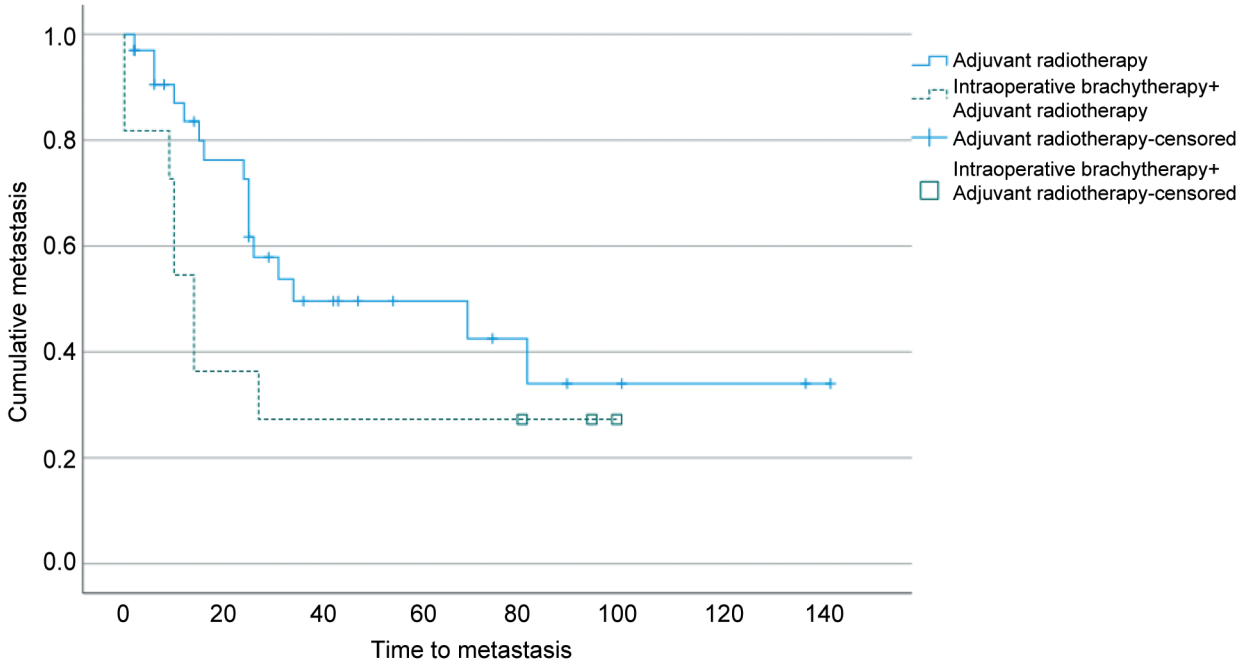

Figure 4. *Time to metastasis for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with adjuvant radiotherapy alone.*

A major limitation of this study is the small number of patients. STSs and LMSs are rare tumors and therefore have a low prevalence, and therefore it is difficult to recruit a sufficient number of patients for high power for statistical analysis. The required number of case reports to achieve the necessary statistical power will hardly ever be reached

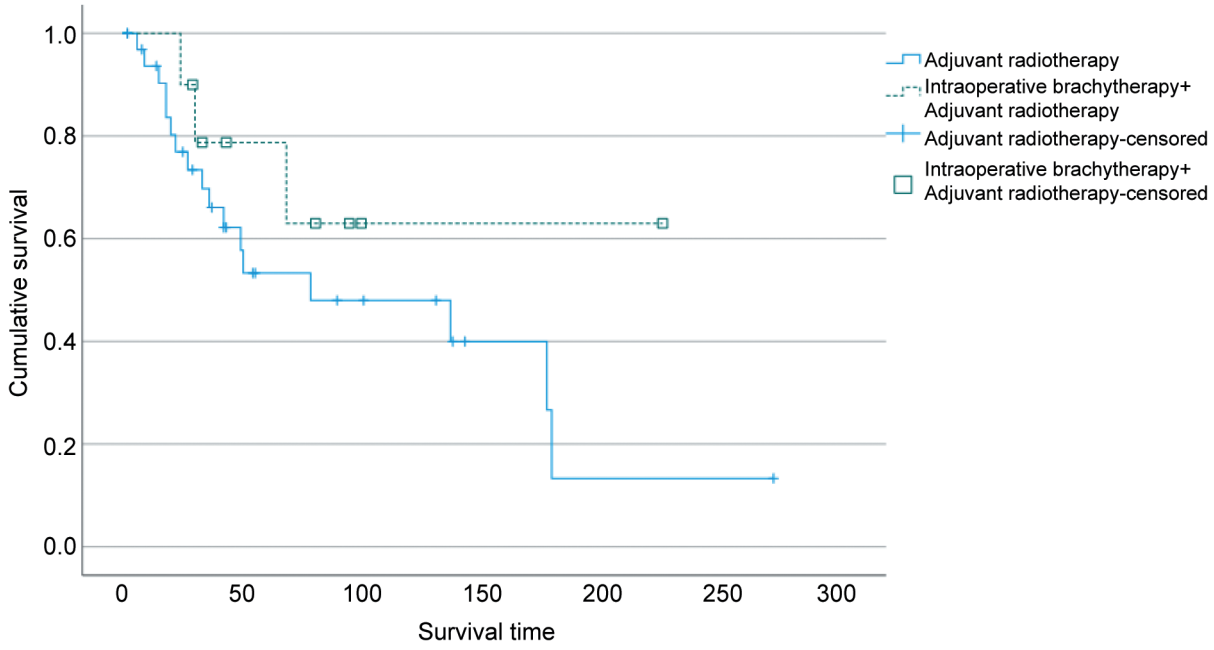

Figure 5. *Survival time for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with adjuvant radiotherapy alone.*

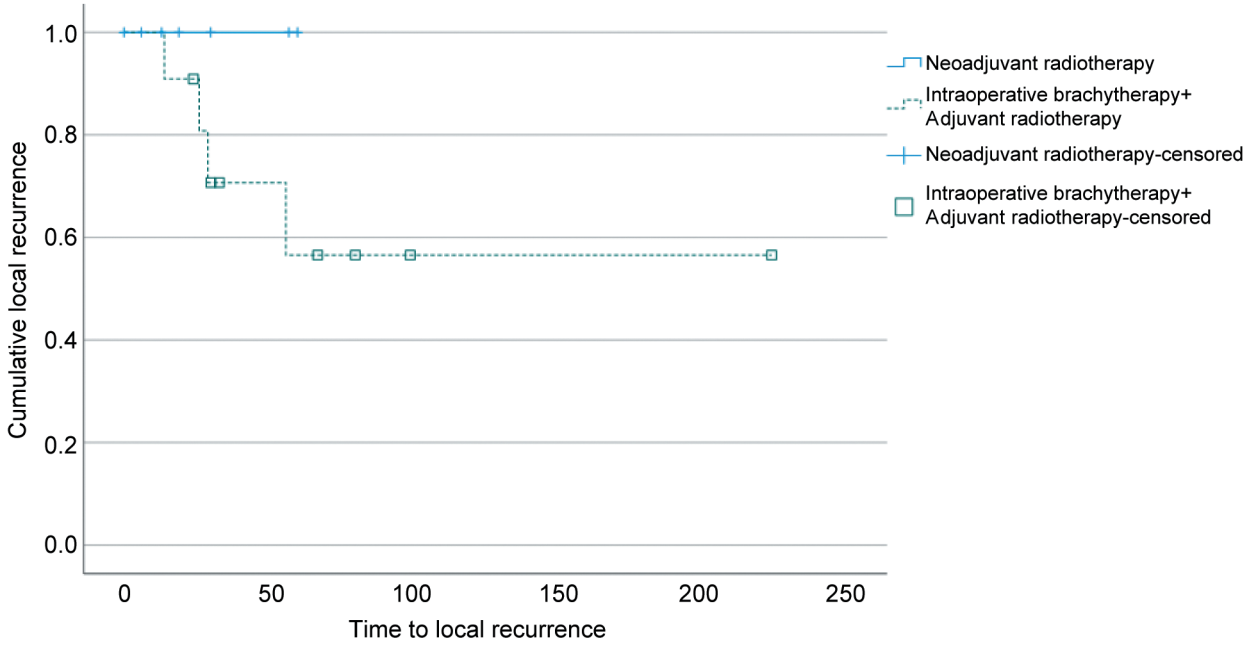

Figure 6. *Time to local recurrence for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with neoadjuvant radiotherapy alone.*

without gathering data internationally. Soft tissue sarcomas constitute a rare type of malignancy, and this applies to an even greater extent to their sub-entity of leiomyosarcomas. Hence, the power for statistical analyses in this retrospective study was low and it could not prove statistically significant advantages of intraoperative BT when compared to other

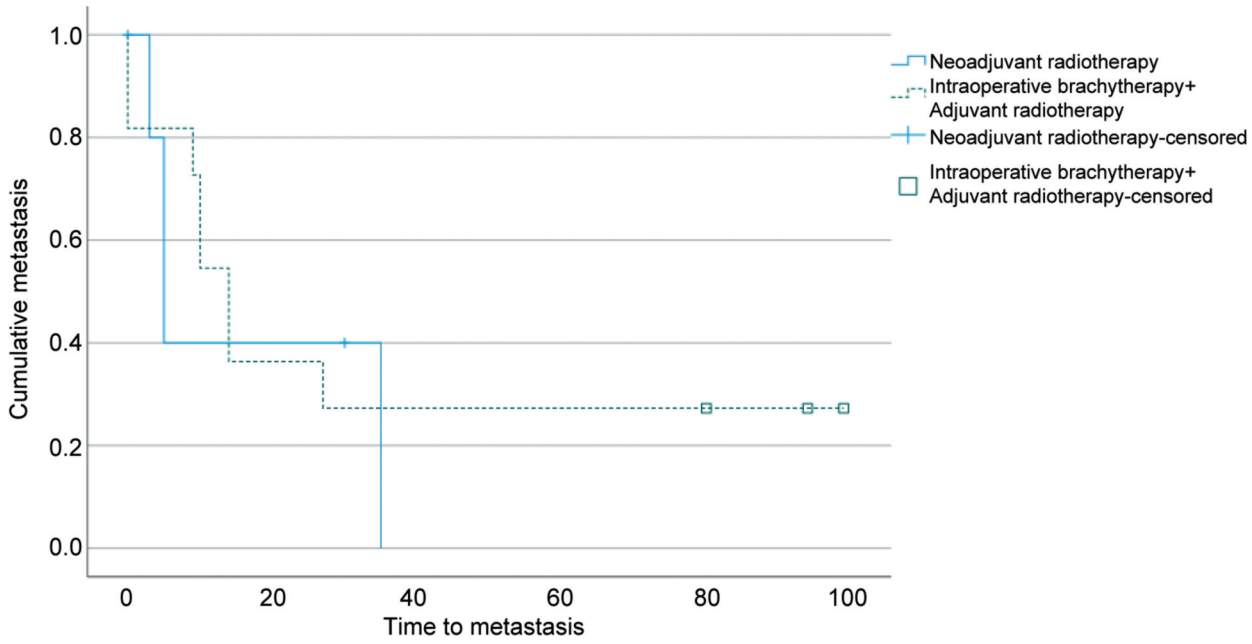

Figure 7. *Time to metastasis for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with neoadjuvant radiotherapy alone.*

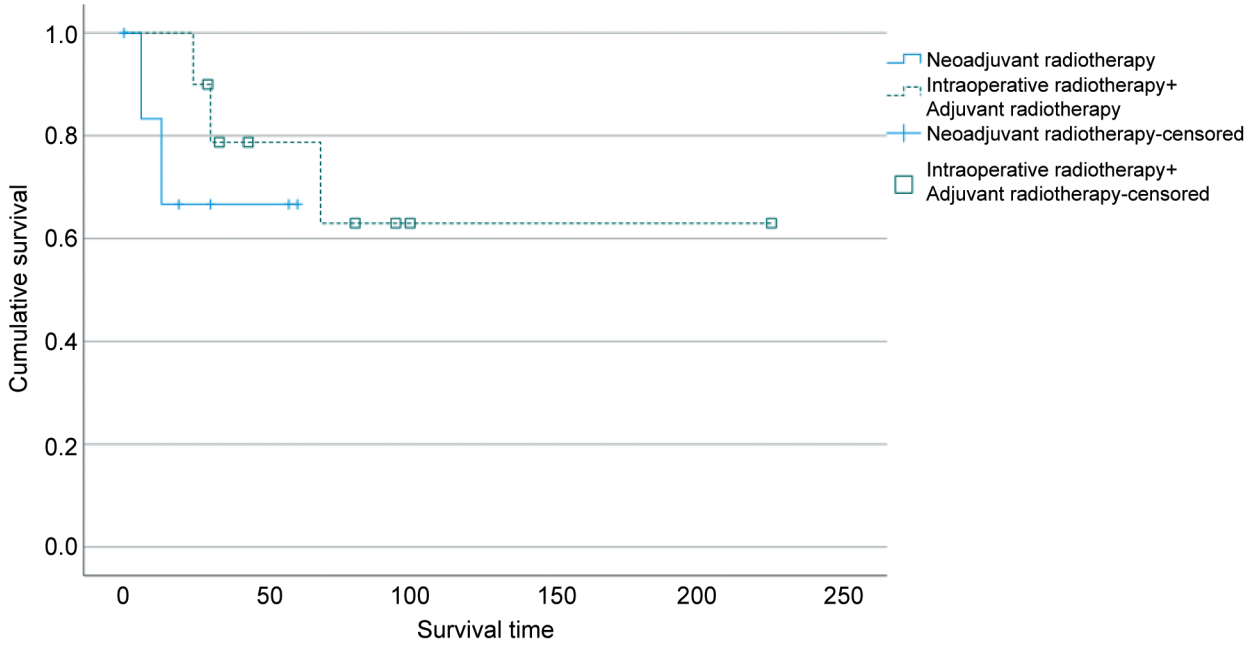

Figure 8. *Survival time for patients treated with intraoperative brachytherapy combined with adjuvant radiotherapy and patients treated with neoadjuvant radiotherapy alone.*

radiation modalities and treatment regimens. Therefore, even though described in the literature, we couldn't achieve favorable results for brachytherapy in this study.

In conclusion, this study showed that additive brachytherapy did not provide a significant advantage in the treatment of leiomyosarcomas. Brachytherapy is seen as an

additive value in the treatment of STSs (LMSs). Even though time-consuming, its place as an additive booster therapy needs to be considered in a multidisciplinary panel. However, this study was limited by the number of patients per treatment group. Larger international multicenter studies are necessary to objectivize the position of brachytherapy in the treatment of leiomyosarcomas on the extremities. Therefore, an active call for gathering data is necessary to give brachytherapy a place in the treatment of STS.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Dammerer Dietmar, Van Beeck Annelies: wrote the article, review of the statistics; Wabro Katrin: review of literature; Blockhuys Karen: statistical analysis; Michielsen Jozef: review of article.

Acknowledgements

The Authors would like to thank Bilal Kapanci, Felix Shumelinsky, Thomas Schubert and Michiel Van de Sande for providing their data.

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Received June 17, 2022
Revised July 10, 2022
Accepted July 20, 2022