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Scientific Article

# Preoperative Ultrahypofractionated Radiation Therapy for Soft Tissue Sarcomas: Low Rate of Wound Complications

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**Purpose:** Normofractionated preoperative radiation therapy (nRT) with 50 Gy applied in 25 fractions represents the most widely used radiation therapy (RT) regimen in combined local treatment of soft tissue sarcomas (STSs). STSs are characterized by a low $\alpha/\beta$ ratio of 4 to 5 Gy, which may translate into a higher sensitivity for hypofractionation. Increasing data from cohorts and phase 2 trials on ultrahypofractionated RT (uhRT) regimens are available. We prospectively assessed our preoperative uhRT sarcoma patient cohort with a focus on short-term wound complications (WCs).

**Methods and Materials:** This is a prospective registry analysis of a single-center patient cohort, treated from 03.2020 to 10.2023 with uhRT (25 Gy in 5 fractions in 1 week). The same radiation oncologists (G.S./C.G.) and surgeon (B.F.) performed the treatment (61/61 and 58/60), as well as the same reference pathologist (B.B.) confirmed all histopathologic diagnoses. WC (according to CAN-NCIC-SR2 trial) and intermediate local control (LC) rates were assessed and compared with outcome data of a previously published cohort of 67 extremity/trunk sarcoma patients treated with nRT by the same authors (7% WC, 98% LC at 3 years).

**Results:** After a mean/median follow-up of 19/19 months (range, 0-46), LC at 1.5 years was 94%. Surgery was performed at a mean/median of 20/16 days (range, 4-60) after uhRT completion. WC were observed in 7/60 operated patients (12%), and in 5/51 (10%) extremity/trunk lesions. Early tolerance was excellent, limited to G0 to G1, even in 3 patients with prior RT to the same region. Clear resection margins were achieved in 55/60 patients (92%). Pathologic necrosis of ≥95% was reported in 5% and 75% achieved less than 50% necrosis.

**Conclusions:** These results show low rates of WC and high LC for uhRT and are comparable with our previously published nRT data. This study supports the routine use of preoperative uhRT for STS.



## Introduction

Ultrahypofractionated radiation therapy (uhRT) is noninferior regarding efficacy and toxicity compared with normofractionated radiation therapy (nRT) in tumor

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entities such as prostate, breast, or rectal cancer.[1-3] Building up on these experiences, uhRT is increasingly being studied for curative combined treatment of soft tissue sarcoma (STS).[4] Several cohort and phase 2 studies show promising results for uhRT with ranging fractionation schedules.[5−18]

STSs are rare heterogeneous tumors with various malignant subtypes, mostly in the upper and lower extremities, trunk wall, or retroperitoneum.[19] Standard treatment of large (≥5 cm) and/or subfascial-located STS is based on surgical resection and radiation therapy (RT) in order to achieve complete remission.[20] The addition of adjuvant RT to surgery in STS translates into roughly 30% reduction of local recurrence probability, whereas no effect is evident on metastatic spread or overall survival rates.[21] Preoperative RT is favored over postoperative RT because of substantially reduced late side effects. In addition, potential tumor downsizing prior to surgery may be beneficial.[22,23] However, twice more wound healing complications are reported following preoperative nRT using nonmodulated techniques (35% vs 17%).[22] The technological evolutions of linear accelerators through intensity modulated radiation therapy (IMRT)[24] and volumetric modulated arc therapy (VMAT) allow highly conformal dose delivery, which translates to an optimized sparing of surrounding normal tissues and, in consequence, substantially less side effects.[25] Preoperative nRT in sarcoma patients using IMRT/VMAT has been reported to reduce related wound healing complications.[26,27] The additional use of image guided radiation therapy allowing reduced RT planning target volumes (PTVs) may further improve tolerance while not compromising disease control.[28]

The historically most widely used preoperative nRT scheme includes a total dose of 50 Gy delivered in 25 fractions (f) over 5 weeks.[20] Radiobiological evaluations in STS found a low $\alpha/\beta$ ratio (<10), suggesting STS to be more susceptible to increased fraction sizes.[29] Recent reports show a low average $\alpha/\beta$ ratio of 2 to 4 Gy with a wide distribution between different sarcoma subtypes, even suggesting further differentiation between subtypes regarding fractionation schemes.[30]

Using uhRT, the treatment time of RT is reduced from 5 to 1-1.5 weeks as treatment sessions decreased from 25 to 5. Based on these findings, uhRT shows promise in significantly shortening the total treatment time (TTT) for the entire combined therapy, reducing it from approximately 3 to 4 months to just 1 month. Provided at least comparable outcomes, uhRT is consequently economically beneficial because it reduces direct and indirect treatment costs for patients, hospitals, and insurances.[31] Current guidelines based on historic practices suggest surgical resection being delayed at least for 4 to 8 weeks after RT completion.[20,22] Back in 2014, Koseła-Paterczyk et al[5] reported uhRT followed by immediate surgery showing lower wound healing complications (22%). Similarly, Parsai et al[10] reported acceptable toxicity (18%).

Increasing reports on mild hypofractionated or uhRT data from phase 1/2 studies and patient cohorts consistently confirm comparable outcomes with preoperative nRT for wound complications (WCs) and disease control.[4]

However, the current literature on uhRT for STS shows noninferiority compared with nRT. Surveys among multidisciplinary sarcoma experts recently showed that only 10% of sarcoma centers regard 5 fractions (25-30 Gy) as the standard treatment of STS.[32]

At our center, preoperative uhRT for STS was implemented in March 2020; patients were consecutively enrolled in this prospective registry. This outcome analysis includes a comparison with relevant uhRT literature and own data from a previously published extremity/trunk-only cohort treated with preoperative nRT.[27]

## Methods and Materials

### Patient cohort

Starting in March 2020, a prospective registry was set up with predefined planning constraints and outcome parameters. Until October 2023, 61 consecutive patients received uhRT with 5 × 5 Gy, of which 3 underwent previous RT. All RTs were performed or supervised by authors G.S. and/or C.G. at the Department of Radiation Oncology, Cantonal Hospital Lucerne. Surgery was performed by author B.F. unless the patient requested external treatment.

All histologic diagnoses were confirmed by reference pathologist author B.B. Initial tumor staging included magnetic resonance imaging (MRI) of the primary lesion and computed tomography (CT) of the chest with or without abdomen. The indication for preoperative RT was discussed and determined in all instances during the weekly Swiss Sarcoma Network (SSN; swiss-sarcoma.net) multicenter sarcoma board meeting. This board comprises multidisciplinary multicenter sarcoma specialists, encompassing surgeons, radiation oncologists, oncologists, diagnostic radiologists, and pathologists.

### Preoperative RT

#### Margins

Definition of PTV/gross tumor volume (GTV) was extrapolated from RTOG 0630.[33] Fusion of MRI image with planning CT was performed to best identify GTV and surrounding edema zone, which was systematically included in the PTV.

#### Contouring

- GTV: tumor volume on MRI without peritumoral edema
- Final GTV: GTV + peritumoral edema

- PTV: final GTV + margins up to 1.5 cm in all directions, +3 to 4 cm in longitudinal direction.

In order to spare the surrounding normal tissues, particularly bone and noninvolved skin, individual manual PTV editing has been performed in all patients.

### Bolus material ("flab")

In patients with superficial tumors, a bolus material (1 cm thickness) was placed to reach the prescribed dose to the affected skin area. To combat any possible microscopic spread caused by the initial biopsy, a bolus was positioned over the biopsy incision.

### RT delivery

The standard RT modality was VMAT with a treatment application based on image guided radiation therapy. Depending on anatomic extension, the use of conformal 3-dimensional (3D) RT was explored (VMAT-equivalent planning target volume dose coverage).[27] In these cases, comparative planning was used to ensure the best possible approach was chosen. In all patients, uhRT was applied on consecutive workdays. The prescribed total dose was delivered with 95% isodose and a max dose (Dmax) of 107% to the PTV. If no bolus was placed, Dmax to the skin was 25 Gy. Doses of >20 Gy to long bones were limited to half the cortical circumference. Of 30 cases with tumors close to the femur or humerus, 4 showed bony tumor invasion. Excluding these 4 cases, dose constraints included Dmax of <26 Gy to the bone.

## Surgery and histopathologic analysis

If logistically possible, we opted for prompt surgical intervention after RT, ideally within the first 2 weeks after RT completion. At the patient's request, 2 patients were operated on externally. Initial diagnosis and excised specimens were histopathologically confirmed and examined on microscopic margins and tumor necrosis by author BB. An unplanned previous excision without histopathologic confirmation of diagnosis and/or without prior MRI or CT ("*whoops* lesions") was performed externally in 9 patients (15%). One patient who experienced a "*whoops*" surgery, resulting in a large residual mass, developed significant local and distant disease progression under RT and was in consequence treated palliatively with chemotherapy. This patient died of progressive local and distant disease undergoing no further surgery. The remaining 60/61 cases were assessable to the WC analysis.

## Chemotherapy

Chemotherapy was delivered in 2/61 uhRT patients prior to RT and surgery. No simultaneous systemic treatment was performed during RT. In the event of new metastatic progression following RT and surgery, the use of chemotherapy was evaluated on a case-by-case basis and not further studied in this analysis.

## Follow-up

Clinical follow-up (FU) after surgery was performed every 3 months in the first 2 to 3 years and later expanded to every 6 months. Surveillance included MRI of the primary tumor site and a CT of the thorax. The choice of imaging in metastasized patients was made based on their individual situation and needs.

## Outcome definitions

The primary goal was to assess early WC rates in the first postoperative 120 days, according to the Canadian NCIC SR2 trial.[22] These include seroma aspiration, antibiotics, revision surgery for wound repair, secondary vacuum-assisted closure, and major wound infections. In addition, early/intermediate disease control and histopathologic necrosis were assessed.

## Statistical analysis

When feasible, standard descriptive statistics (mean/median/range) were used. Kaplan-Meier survival curves were used for local recurrence, distant metastatic-free survival, and overall survival. Metastatic-free survival is defined by the absence of distant progression whereby patients with previous metastatic disease were excluded from the related analysis.

# Results

Patient and disease characteristics of the current uhRT and previously published nRT cohort[27] are shown in Table 1.

## Radiation treatment and tolerance

Fifty-four of 61 lesions were irradiated with VMAT, 7 using 3D-conventional techniques with IMRT-equivalent dose distribution. All patients completed the prescribed short course uhRT. In 1/26 cases with a tumor near the femur or humerus but without bone involvement, the maximum dose to the cortical bone was 26.6 Gy, surpassing the prescribed Dmax of <26 Gy.

Early actinic reactions were limited to G0 to G1 dermatitis (grade 0-1 skin reaction, National Cancer Institute

**Table 1 Patient and disease characteristics of the current uhRT vs previously published nRT cohort[27]**

| Parameters | uhRT | nRT[27] |
|---|---|---|
| No. of patients | 61 | 67 |
| Total RT dose | 25 Gy | 50 Gy |
| Dose/fraction | 5 Gy | 2 Gy |
| Prescribed RT duration | 1 wk | 5 wk |
| Mean/median FU (mo) | 19/19 | 37/33 |
| Diagnosis | | |
| Myxofibrosarcoma | 14 | 6 |
| Myxoid liposarcoma | 8 | 21 |
| Dedifferentiated liposarcoma | 7 | 2 |
| Leiomyosarcoma | 5 | 3 |
| Unclassified pleomorphic | 17 | 17 |
| Others | 10 | 18 |
| M+ at primary staging | 6 | N/A |
| N+ at primary staging | 3 | N/A |
| Previous local treatment | 15/61 (25%) | 14/67 (21%) |
| "*Whoops*" surgery | 9 (15%) | 14 (21%) |
| Previous surgery, no RT | 3 (5%) | N/A |
| Previous surgery + RT | 3 (5%) | 0 |
| Locally Tx-naive patients | 46/61 (75%) | 53/67 (79%) |
| Induction chemotherapy | 2 | N/A |
| Mean/median (range) interval RT surgery (wk) | 2.9/2.3 (0.6-8.6) | 7.3/7 (3-12) |
| TTT (RT start to date of surgery, d) | 26/23 (10-75) | N/A |
| Resection status | | |
| R0 | 55 | 66 |
| R1 | 5 | 1 |
| R2 | 0 | 0 |
| No surgery | 1 | 0 |
| LVA | 11 | 0 |
| %Tumor necrosis, mean/median (range) | 29/15 (0-100) | N/A |

*Abbreviations:* FU = follow-up; LVA = lymphaticovenous anastomosis; M+ = distant metastasis; N+ = nodal metastasis; N/A = not available; nRT = normofractionated radiation therapy; RT = radiation therapy; Tx = therapy; TTT = total treatment time; uhRT = ultrahypofractionated radiation therapy.

Common Terminology Criteria for Adverse Events), even among all 3 patients with previous RT to the same region. Radiation-induced late effects (>3 months after RT) related to RT were not observed based on consequent FU visits performed by the involved surgeon (author B.F.).

## Surgery

Immediate surgical intervention was anticipated, ideally within 14 days, based on the capacity of the operating room (OR) and the availability of the surgeon. En bloc resection of macroscopic tumor was performed 0.6 to 8.6 weeks after uhRT completion by author B.F. Longer intervals from completion of uhRT until surgery were mainly defined by COVID-19 pandemic–related lack of OR capacity.

## Histopathologic findings

### Surgical margins

Metric margins are shown in Table 2. Marginal resection (R1) was reported in 5/60 operated patients. In 2

**Table 2 Analysis of surgical margins**

| Parameters | Clear margins (RO) | | | | Marginal resection (Rl) | Intralesional resection (R2) | No surgery |
|---|---|---|---|---|---|---|---|
| | 0-1 mm | >1-2 mm | >2-5 mm | >5 mm | | | |
| All (61) | 28 | 9 | 7 | 11 | 5 | 0 | 1 |
| "*Whoops*" surgery (9)<br>*5/9 with residual tumor* | 3 | 0 | 0 | 4 | 1 | 0 | 1 |
| Previous surgery, no RT (3) | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| Previous surgery + RT (3) | 2 | 0 | 0 | 0 | 1 | 0 | 0 |
| Locally naive (46) | 22 | 9 | 7 | 6 | 2 | 0 | 0 |

*Abbreviation:* RT = radiation therapy.

cases, external surgery was performed according to the patient's wishes. Clear margins were achieved in 55/60 (92%), with margins of 0 to 1 mm in 28/60 (47%) patients. Clear margins were achieved in 11/14 (79%) patients with prior "*whoops*" surgery or initial surgery with or without radiation for previous sarcoma.

**Table 3 Characteristics of operated patients affected by WC**

| Parameters | N | WC (%) | Characteristics of WC affected patients |
|---|---|---|---|
| Primary site | | | |
| Extremity/chest wall | 51 | 5/51 (10%) | 1/5: following previous IC<br>1/5: following *whoops* surgery of foot lesion, with previous wound healing disorder, because of substantial arteriosclerosis, 91 y<br>1/5: following fourth OP for third LR |
| Pelvic/retroperitoneal/abdominal wall | 9 | 2/9 (22%) | Very large abdominopelvic PTVs (1487 $cm^3$ and 2960 $cm^3$) |
| Previous treatment | | | |
| "*Whoops*" | 8 | 1/8 (13%) | |
| Previous surgery, no RT | 3 | 1/3 (33%) | |
| Previous surgery + RT | 3 | 0/3 (0%) | |
| Induction chemotherapy | 2 | 1/2 (50%) | |
| None | 44 | 4/44 (9%) | |
| Time between RT and surgery (wk) | | | |
| 0-2 | 12 | 1/12 (8%) | |
| 2-4 | 37 | 3/37 (8%) | |
| 4-8 | 10 | 3/10 (30%) | |
| 8< | 1 | 0/1 (0%) | |
| Surgical characteristics | | | |
| Surgical flab transplants | 25 | 4/25 (16%) | |
| LVA | 11 | 2/11 (18%) | 1/2 following IC, 1/2 following fourth surgery for recurrence |
| Flab (= prescription dose to skin) | | | |
| Yes (>15 $cm^3$) | 37 | 4/37 (11%) | |
| No | 23 | 3/23 (13%) | |
| TOTAL | 60 | 7/60 (12%) | |

*Abbreviations:* IC = induction chemotherapy; LR = local recurrence; LVA = lymphaticovenous anastomosis; OP = operation; PTV = planning target volume; RT = radiation therapy.

**Table 4 Characteristics of WC**

| Patients | PTV ($cm^3$) | PTV ($cm^3$) | Bolus material ($cm^3$) | Anatomic l ocalization | Time between RT and surgery (d) | WC postsurgery (d) | Duration of WC (wk) | Previous treatment | Surgical flab | Type of troubles | Management of troubles | Outcome of WC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pat. 1 | 89 | 24 | 100 | Foot | 33 | 14 | 8 | None | No | Necrosis | VAC | Ad integrum, no consequences |
| Pat 2 | 894 | 147 | 84 | Dorsal thigh | 14 | 22 | 4 | None | No | Seroma, infection | Wound revisions, debridement, VAC | Ad integrum, no consequences |
| Pat 3 | 1171 | 31 | 0 | Lateral Thigh | 30 | 34 | 4 | 3 × previous surgery | No (flap for revision) | Extensive seroma, prolonged wound healing | D ebridement, VAC, flap plastic | Ad integrum, no consequences |
| Pat 4 | 2960 | 1195 | 0 | Abdominal wall | 21 | 6 | 5 | None | Yes | Seroma, infection | Wound revision | Ad integrum, no consequences |
| Pat 5 | 1487 | 156 | 60 | Fossa ischiorektalis | 36 | 10 | 12 | None | Yes | Seroma, infection + ileus | Debridement VAC + laparotomy | Ad integrum, no consequences |
| Pat 6 | 1445 | 390 | 158 | Medial thigh | 24 | 40 | 0.5 | Induction chemotherapy | Yes | Seroma, dehiscence, fistula | Wound revision, debridement | Ad integrum, no consequences |
| Pat 7 | 170 | 11 | 12 | Foot | 9 | 11 | 6 | "*Whoops*" surgery | Yes | Sepsis, prolonged wound healing even prior to RT because of peripheral vascular disease | Debridement (2 ×), antibiotics | Ad integrum, no consequences |

*Abbreviations:* GTV = gross tumor volume; Pat = patient; PTV = planning target volume; RT = radiation therapy; VAC = vacuum-assisted closure; WC = wound complication.

### Tumor necrosis

In one case, necrosis was not assessable because no surgery was performed. In the second case, a skin leiomyosarcoma was previously treated by "*whoops*" surgery resulting in an insufficient amount of tumor residuum for necrosis analysis. The 2 patients treated with preoperative induction chemotherapy showed a necrosis rate of 80% and 90%. Further analysis focuses on patients without prior chemotherapy. The percentage of tumor necrosis was mean/median 29%/15% (range, 0-100) following preoperative uhRT. Five of 57 (9%) cases achieved ≥90% necrosis, and 3/57 (5%) achieved ≥95% necrosis. Nine of 57 (16%) achieved between 50% to 90% necrosis, and 43/57 cases (75%) achieved less than 50% necrosis.

## Wound complication rate

Despite conservative approaches with seroma aspiration and antibiotics, all observed wound complications led to secondary revision in the first 3 months after primary surgery and occurred in 7/60 patients (12%) (Table 3).

All affected patients experienced complete WC healing after a mean/median 5.6/5 (range, 0.5-12) weeks from onset (Table 4). There is no significant difference related to PTV, GTV, and bolus deposit (*P* value, 0.82, 0.66, and 0.66) between patients with wound complications and such with none. The area of skin covered by bolus material had a volume ($cm^3$) of mean/median 127/84 $cm^3$ (range, 17-500) among patients without WC compared with mean/median 101/92 $cm^3$ (range, 60-158) in patients with WC. Small boluses less than 15 $cm^3$ were excluded from analysis because they only covered the incision area of the biopsy. PTV among patients without WC was mean/median 1075/816 (range, 65-4350) compared with patients with WC mean/median 1174/1171 (range, 89-2960). GTV among patients without WC was mean/median 361/168 (range, 2-1923) compared with patients with WC mean/median 279/147 (range, 11-1195).

## Disease control

Staging before treatment showed 8/61 (13%) patients with nodal and/or distant metastatic disease. Therefore, these were excluded from the analysis of metastatic-free survival. At the time of analysis, 8/61 patients have died, 6/8 from STS; 10 patients are alive with metastatic disease (Fig. 1). Local recurrence (LR) developed in 3/60 operated patients, 4 to 8 months after uhRT, with related LR-free survival of 94% at 1.5 years (Fig. 1). All 3 patients with local failure received diagnoses of high-grade (G3) STS. Two were in the medial thigh with a GTV of over 1100 $cm^3$. The third was in the arm, treated with R1 resection externally, constituting the patient's second LR. Minimal resection margins were <1 mm throughout of which one was classified as R1. None of them had previous "*whoops*" surgery.

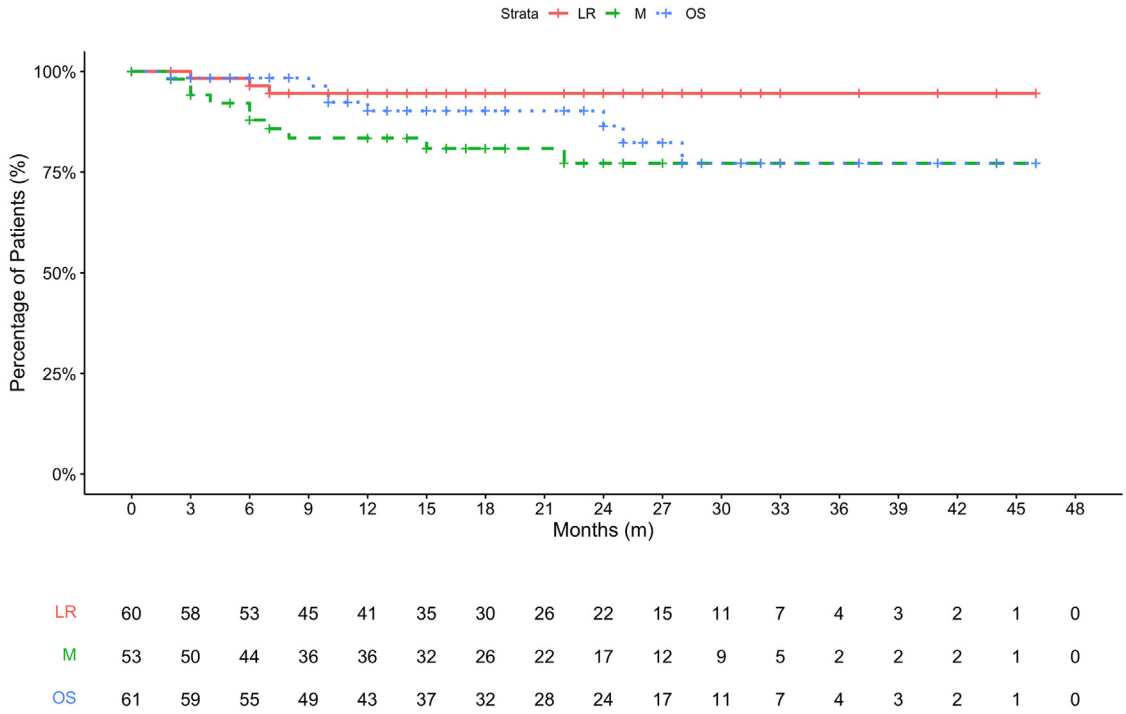


**Figure 1** Kaplan-Meier survival curves for local recurrence (LR), distant metastatic-free survival (M), and overall survival (OS).

**Table 5 Characteristics of selected nRT and uhRT studies**

| | | Author (y), study name | Study | Interval | n | RT (technique) | Chemotherapy | R0 | WC | Time RT to surgery | LC @ y (median FU) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| nRT | 1 | O'Sullivan et al[22] (2002) CAN-NCIC-SR2: Phase III | Phase 3 | 1994-1997 | 94 | 25 × 2 Gy/5 wk (2/3D) | - | 84% | 35% | 3-6 wk | 93% @ 5 y (3.3 y) |
| | 2 | Canter et al[34] (2010) | Prosp cohort | 2000-2009 | 25 | 25 × 2 Gy/5 wk (3D) | - | 84% | 28% | 4-6 wk | 100% @ 3 y (1.6 y) |
| | 3 | Shah et al[35] (2012) | Prosp cohort | 2000-2010 | 30 | 25 × 2 Gy/5 wk (3D) | - | 80% | 23% | 4-6 wk | 100% @ 5 y (3.3 y) |
| | 4 | Wang et al[28] (2015) RTOG-0630 | Phase 2 | 2008-2010 | 79 | 25 × 2 Gy/5 wk (3D 25%/IMRT 75%) | - | 76% | 37% | 4-8 wk | 94% @ 2 y (3.6 y) |
| | 5 | Studer et al[27] (2018) | Prosp cohort | 2008-2016 | 67 | 25 × 2 Gy/5 wk (IMRT) | - | 97% | 7% | 6-8 wk | 98% @ 3 y (2.8 y) |
| uhRT | 1 | Koseła-Paterczyk et al[5] (2014) | Phase 2 | 2006-2011 | 272 | 5 × 5 Gy/5 d (3D or IMRT) | 22% | 79% | 32% | Immediate | 81% @ 3 y (2.9 y) |
| | 2 | Koseła-Paterczyk et al[18] (2016) | Phase 2 | 1999-2014 | 32 | 5 × 5 Gy/5 d (3D) | - | 90% | 22% | 3-7 d | 90% @ 5 y (5 y) |
| | 3 | Kubicek et al[8] (2018) | Phase 2 | N/A | 13 | 5 × 7-8 Gy (Cyber-Knife) | 21% | 100% | 29% | 4-8 wk | 93% @ 9 mo (9 mo) |
| | 4 | Kalbasi et al[11] (2020) | Phase 2 | 2014-2016 | 52 | 5 × 6 Gy/5d (IMRT 76%/3D 20%/Elec-tron 4%) | - | 82% | 32% | 2-6 wk | 94% @ 2 y (2.4 y) |
| | 5 | Parsai et al[10] (2020) | Retrosp cohort | 2016-2019 | 16 | 5 × 6 Gy/5 d (IMRT/VMAT) | 6% | 63% | 31% | 0-7 d | 100% @ 1 y (0.9 y) |
| | 6 | Koseła-Paterczyk et al[6] (2020) NCT03816475 | Phase 2 | 2015-2019 | 27 | 5 × 5 Gy/5 d (3D 62%/IMRT) | - | 93% | 28% | 5-10 wk | 100% @ 3 y (2.3 y) |
| | 7 | Gobo Silva et al[12] (2021) NCT02812654 | Phase 2 | 2015-2018 | 18 | 5 × 5 Gy/5 d (3D or IMRT) | Yes | 83% | 33% | 4-8 wk | 94% @ 3 y (2.4 y) |
| | 8 | Koseła-Paterczyk et al[7] (2016/Update 2021) | Phase 2 | 2010-2017 | 311 | 5 × 5 Gy/5 d (3D 96%/IMRT 4%) | 30% | 84% | 31% | 2-4 d | 86% @ 5 y (4.8 y) |
| | 9 | Spalek et al[9] (2021) NCT03651375 | Phase 2 | 2017-2019 | 46 | 5 × 5 Gy/5 d (IMRT 52%/VMAT 41%/3D 7%) | Yes | 72% | 34% | 6-8 wk | 93% @ 2 y (2 y) |
| | 10 | Potkrajcic et al[14] (2021) | Retrosp cohort | 2018-2020 | 18 | 5 × 5 Gy/5 d (3D 83%/VMAT 7%) | - | 78% | 28% | 4.1 wk (median) | 92% @ 6 mo (5 mo) |

(*continued on next page*)

**Table 5** (*Continued*)

| | Author (y), study name | Study | Interval | n | RT (technique) | Chemotherapy | R0 | WC | Time RT to surgery | LC @ y (median FU) |
|---|---|---|---|---|---|---|---|---|---|---|
| 11 | Savjani et al[15] (2021) UCLA | Phase 2 | 2016-2018 | 52 | 5 × 6 Gy/5 d | - | 80% | 27% | N/A | 93% @ 3 y (3 y) |
| 12 | Bedi et al[16] (2021) NCT02634710 | Phase 2 | 2016-2020 | 32 | 5 × 7 Gy/10 d (1 × /48 h) (3D/ or MRT) | 31% | 91% | 25% | 4-6 wk | 100% @ 3 y (3 y) |
| 13 | Leite et al[13] (2021) | Phase 2 | 2015-2019 | 25 | 5 × 8 Gy/10 d (1 × /48 h) (IMRT/VMAT) | 20% | 96% | 28% | 4-12 wk | 100% @ 2 y (1.8 y) |
| 14 | Mayo[17] (2023) | Prosp cohort | 2016-2020 | 22 | 5 × 6 Gy/5 d (IMRT 9%/VMAT 91%) | 5% | 82% | 41% | 0-5 d | 100% @ 2 y (2 y) |
| 15 | Current Study (2023) | Prosp cohort | 2020-2023 | 61 | 5 × 5 Gy/5 d (IMRT 11%/VMAT 89%) | 3% | 92% | 12% | 2.3 wk (median) | 94% @ 1.5 y (1.6 y) |

*Abbreviations:* FU = follow-up; IMRT = intensity modulated radiation therapy; LC = local control; VMAT = volumetric modulated arc radiation therapy; Prosp = prospective; Retrosp = retrospective; WC = wound complication rate.

## Discussion

This analysis assessed WC rate and early/intermediate LC following preoperative uhRT in sarcoma patients. We found low WC rates and early LC, comparable with our data from a nRT cohort.[27] When focusing solely on current cases in the extremities and trunk to ensure comparability, the prevalence of WC was similar in both cohorts (10% vs 7%). When interpreting the reported WC and LC rates, it is important to consider that 15/60 (25%) patients had undergone either prior "*whoops*" surgery or initial surgery with or without radiation for a previously diagnosed STS.

Apart from its nonrandomized settings, this work has limitations in terms of sample size, number of events, and the short FU period for assessing LC.

The use of preoperative uhRT for STS has been increasing over the past years. Study protocols show some heterogeneity regarding fractionation, additional use of chemotherapy, and the time interval between RT and surgery. Authors reporting on uhRT before 2020 often opted for 5 × 5 Gy. Over the past few years, different groups published 5 × 6 to 8 Gy schemes, with smaller sample sizes and shorter FU (Table 5).

WC rates were reported to be 18% to 34% following uhRT using 5 × 5 Gy, 11% to 32% following moderate hypofractionated RT (mhRT),[36–38] and 30% to 36% following nRT. The latter was partly treated in the pre-IMRT era, whereas our own collective is based on VMAT (-equivalent) treatment plans and restrictive PTV definitions recommended by the RTOG-0630 trial.[28,33] The listed 6 analyses using higher doses (5 × 6-8 Gy) resulted in WC rates between 24% and 32% and LC rates of 93% to 100%. Following uhRT, our own WC rate falls within the lower range of the spectrum.

A substantial number of our operated patients had narrow surgical resection margins of 0 to 1 mm (28/60) and 0 to 2 mm (37/60). Although often associated with increased concerns regarding the possibility of residual cancer cells, these narrow resection margins appear to indicate the compensatory effect of uhRT.

Reported uhRT LC rates range between 80% and 100% at 3 to 5 years after primary treatment and compare with roughly 93% in the prospective randomized nRT trials at 3 to 5 years FU. Previously published uhRT LC rates match well with our own results of 94% after a still short mean FU of 1.5 years.[4] Trials using mhRT show slightly lower local control, although the variability is high. Using 8 × 3.5 Gy treatment scheme as Ryan[39] in 2008, MacDermed[40] in 2010, Pennington[41] in 2018, and Lu[37] in 2018, LC between 87% and 89% was achieved at 2 to 5 years. With a short FU time of 16 months (median), Guadagnolo[38] published in 2022 promising results using a dose of 42.75 Gy in 15 fractions on 119 patients, resulting in 93% LC at 2.5 years.

Roohani et al[4] stated in a recent systematic review (2022) that uhRT translates to reduced rates of acute toxicity compared with nRT. This is strongly supported by our own cohort with no G2 or higher acute actinic effects (in 2 cases with involved skin). Kao[42] published a recent meta-analysis on preoperative uhRT of prospective studies stating uhRT being feasible and well tolerated.

Using uhRT reduces the radiation treatment time by 4 weeks, increasing patients' comfort and economic efficiency.[31] Substantially less acute (skin) reaction allows for immediate surgery after uhRT and avoids the onset of fibrotic changes. This shortens the TTT to 2 to 3 weeks instead of 2 to 3 months. In addition, this approach makes preoperative radiologic restaging unnecessary. In 2014, Koseła-Paterczyk first described immediate surgery after uhRT for STS, which was also incorporated into the treatment scheme of Parsai in 2020 and Mayo in 2023.[5,10,17] Immediate surgery is reported as a safe option, considering the very high short-term treatment tolerance.[43] This is confirmed by our own cohort results.

Tumor necrosis has been reported as a predicting parameter for local and distant control, as well as overall survival.[40,44–47] We achieved a median necrosis rate of 15%, lower than that in comparable studies with conventional fractionation (25%/30%/35%/59%).[34,35,46,48] Following an interval of 41 days from RT (using 7 × 5 Gy with 31% received neoadjuvant chemotherapy) to surgery, Bedi et al[16] published similar results with 12.5% of cases achieving ≥90% necrosis compared with 9% in our cohort. We achieved complete pathologic necrosis at ≥95% in 5% of our patients compared with other publications using preoperative ifosfamide/doxorubicin chemotherapy, with 19%[41] and 24%.[9] We explain our low rate of substantial necrosis by the absence of chemotherapy and a shorter interval between RT completion and surgery (median 16 days). There are no data on the necrosis rate and its significance after neoadjuvant uhRT without chemotherapy and immediate surgery.

## Conclusion

Our analysis shows low WC and high LC rates of preoperative uhRT and nRT in patients with STS. uhRT translates to a TTT of roughly 1 month compared with 3 to 4 months in nRT, reducing the treatment burden on patients and medical facilities, besides increased economic efficiency.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT (OpenAI) in order to draft and edit text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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