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CLINICAL INVESTIGATION **Bone**

LOCAL THERAPY IN LOCALIZED EWING TUMORS: RESULTS OF 1058 PATIENTS TREATED IN THE CESS 81, CESS 86, AND EICESS 92 TRIALS

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Purpose: The impact of different local therapy approaches on local control, event-free survival, and secondary malignancies in the CESS 81, CESS 86, and EICESS 92 trials was investigated.

Methods and Materials: The data of 1058 patients with localized Ewing tumors were analyzed. Wherever feasible, a surgical local therapy approach was used. In patients with a poor histologic response or with intralesional and marginal resections, this was to be followed by radiotherapy (RT). In EICESS 92, preoperative RT was introduced for patients with expected close resection margins. Definitive RT was used in cases in which surgical resection seemed impossible. In CESS 81, vincristine, adriamycin, cyclophosphamide, and actinomycin D was used. In CESS 86, vincristine, adriamycin, ifosfamide, and actinomycin D was introduced for patients with central tumors or primaries >100 cm^3. In CESS 92, etoposide, vincristine, adriamycin, ifosfamide, and actinomycin D was randomized against vincristine, adriamycin, ifosfamide, and actinomycin D in patients with primaries >100 cm^3.

Results: The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT ($p = 0.001$). Event-free survival was reduced after definitive RT ($p = 0.0001$). Irradiated patients represented a negatively selected population with unfavorable tumor sites. Definitive RT showed comparable local control to that of postoperative RT after intralesional resections. Patients with postoperative RT had improved local control after intralesional resections and in tumors with wide resection and poor histologic response compared with patients receiving surgery alone. Patients with marginal resections with or without postoperative radiotherapy showed comparable local control, yet the number of patients with good histologic response was higher in the latter treatment group (72.2% vs. 38.5%).

Conclusion: Patients with resectable tumors after initial chemotherapy had a low local failure rate. With preoperative RT, local control was comparable. RT is indicated to avoid intralesional resections. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative RT may improve local control.

Ewing tumor, Local therapy, Postoperative radiotherapy, Preoperative radiotherapy.

INTRODUCTION

The Cooperative Ewing's Sarcoma Studies (CESS) 81 and 86 and the European Intergroup Ewing's Sarcoma Study 92 (EICESS 92) used a multimodal treatment approach that included chemotherapy, surgery, and radiotherapy (RT) (1–3). Local therapy was not randomized but tailored to the individual patient and tumor characteristics. When a marginal or wide resection seemed possible, local therapy included tumor resection. RT alone was used in unresectable tumors (4, 5). None of the Ewing's sarcoma trials evaluated the options of surgery alone, RT alone, or a combination of both in a randomized design (6–9). Hence, the question of the best local therapy modality is at present unresolved. On the basis of the large accrual of the German and subsequently European Ewing's sarcoma trials between 1981 and 1999, the impact of different local treatment strategies on local control and event-free survival (EFS) was analyzed, focusing on the role of definitive RT and combined surgery and RT. Furthermore, the impact of local therapy modalities on secondary malignancies was evaluated.

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Table 1. Definition of Enneking criteria

Term	Definition
Radical resection	Whole tumor-bearing compartment removed en bloc
Wide resection	Tumor and its pseudocapsule removed en bloc surrounded by healthy tissue within the tumor-bearing compartment
Marginal resection	Tumor is removed en bloc; however, the line of resection runs through the pseudocapsule of the tumor; microscopic residual disease is likely
Intralesional resection	Tumor opened during surgery, surgical field contaminated; microscopic or macroscopic residual disease is present

METHODS AND MATERIALS

This retrospective analysis included 1058 patients with nonmetastatic Ewing's sarcoma, atypical Ewing's sarcoma, or malignant primitive neuroectodermal tumors treated according to the CESS 81, CESS 86, and EICESS 92 trials. The first diagnosis of the disease was between 1981 and 1999. For the purpose of this analysis, 68 patients of the pilot trial CESS 86P were grouped with the patients treated according to the CESS 86 protocol, and 81 patients of the pilot trial CESS 91P were grouped with those treated according to the EICESS 92 protocol. A total of 654 protocol patients fulfilled all formal study criteria (1–3). The analysis also included 404 follow-up patients who were treated according to the trial guidelines but who started therapy >3 weeks after biopsy, who were entered >6 weeks after initiation of treatment, who were >25 years (CESS 81 and 86) or >35 years (EICESS 92), or who started treatment with definitive local therapy. Nineteen patients were lost to follow-up immediately after therapy and were excluded from the analyses regarding outcome.

Criteria determining choice of local treatment

Treatment consisted of combination chemotherapy and local therapy (i.e., surgery with or without postoperative RT, RT alone, or preoperative RT). Local therapy was performed after neoadjuvant chemotherapy. The choice of local treatment was not randomized but was decided by the local investigator and a local therapy advisory board depending on the individual characteristics of each patient's disease. Surgery was performed when a nonmutilating wide or marginal resection according to the Enneking classification (10) (Table 1) was feasible. In CESS 81, postoperative RT was given when parts of the resected tumor-bearing bone remained *in situ* or when nonradical surgery was performed. In CESS 86 and EICESS 92, patients with marginal or intralesional resection and patients with a poor response to initial chemotherapy (>10% viable tumor cells in the resected tumor [11]) received postoperative RT. Definitive RT was preferred when surgery would only allow intralesional resection or a debulking procedure. In EICESS 92, preoperative RT was introduced as a new local therapy modality in patients with expected close resection margins and when additional tumor reduction was expected to facilitate function-preserving surgery.

Radiation dose and fractionation

In CESS 81, 46–60 Gy was applied for definitive RT with conventional fractionation (1.8–2 Gy/d). Postoperatively, 36 Gy was given to patients with incomplete resection of the involved bone or with incomplete tumor resection.

In CESS 86, the radiation doses were 60 Gy for definitive RT and 44 Gy for postoperative RT after marginal and wide resection or 60 Gy in the case of intralesional resection. Patients who received either definitive or postoperative RT were randomized to conventional fractionation (2 Gy/d) vs. a hyperfractionated accelerated split-course regimen using 1.6 Gy twice daily with a 10-day break after 22.4 Gy. In view of poor local control in the irradiated patients of the CESS 81 trial, CESS 86 introduced centralized RT review. Conventionally fractionated RT was applied concomitantly with chemotherapy, omitting adriamycin or actinomycin D. Patients who underwent hyperfractionated RT received the full cytotoxic regimen. Some institutions were, however, hesitant to give actinomycin D and adriamycin during the break of the RT split.

In the EICESS 92 trial, 54 Gy was applied to patients receiving RT alone. In postoperatively irradiated patients, 44 Gy or 54 Gy was given depending on the extent of the previous surgery and histologic response (i.e., 44 Gy in the case of a wide resection and poor histologic response or marginal resection and good histologic response, and 54 Gy in the case of a marginal resection and poor histologic response or intralesional resection). Again, patients were randomly allocated to conventional or hyperfractionated accelerated fractionation for definitive and postoperative RT. For preoperative RT, 44 Gy was applied when a wide resection was anticipated and 54 Gy was given when a marginal or intralesional resection was expected. This was administered as a hyperfractionated split course with 1.6 Gy twice daily and a 10-day break after 22.4 Gy.

Treatment volume

In CESS 81, the whole tumor-bearing compartment was irradiated to a dose of 36 Gy. In patients who underwent definitive RT, shrinking fields encompassing the initial tumor extent and an additional 5-cm margin were used after 36 Gy. In CESS 86 and EICESS 92, the volume of RT consisted of the pretherapeutic tumor size plus a 5-cm margin. The boost volume for doses >44 Gy was applied to the pretherapeutic tumor size plus a 2-cm margin.

Chemotherapy

In CESS 81, chemotherapy consisted of four 9-week courses of vincristine, adriamycin, cyclophosphamide, and

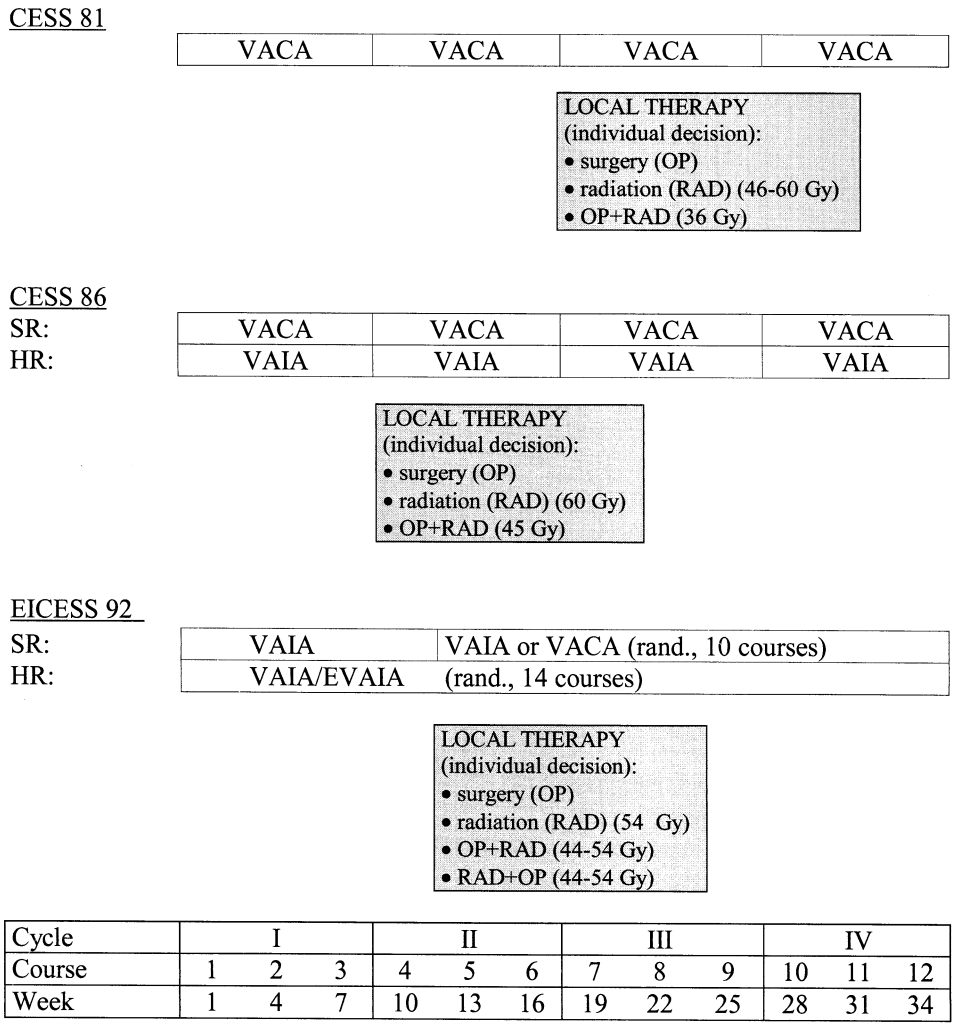

Fig. 1. Systemic and local therapy modalities in CESS 81, CESS 86, and EICESS 92. SR = standard-risk patients; HR = high-risk patients.

actinomycin D (VACA). In CESS 86, patients classified as at standard risk with nonmetastatic tumors of the extremity and <100 cm^3 initial volume received VACA, all other patients received ifosfamide instead of cyclophosphamide (VAIA). In EICESS 92, standard-risk patients (nonmetastatic and <100 cm^3 initial tumor volume) had four 3-week courses of VAIA and were then randomized to receive another 10 courses of either VACA or VAIA. High-risk patients (metastatic or ≥ 100 cm^3 initial tumor volume) were randomized to receive either VAIA or VAIA plus etoposide (EVAIA). Additional details of systemic treatment have been published elsewhere (1, 3, 12, 13). Figure 1 gives an overview of the different chemotherapy and RT modalities of the three trials.

Statistical analysis

EFS was estimated using the Kaplan-Meier method. Statistical significance was evaluated with the log–rank test. The following were considered events in terms of EFS when occurring as first events: local relapse, systemic relapse, death from any reason, and secondary neoplasm. The cumulative incidence of local relapse was estimated using the competing risk analysis (14, 15). The distributions of clinical factors at diagnosis and treatment characteristics were compared using the Mann-Whitney *U* test and chi-square test. The median follow-up from diagnosis to the date of analysis was 107 months.

RESULTS

Table 2 lists the patient characteristics according to type of local therapy. No statistically significant differences were found between groups concerning initial tumor size, gender, and median age. Of the patients who received definitive RT, 70.7% presented with an axial tumor site. The corresponding numbers for those who underwent surgery with or without postoperative RT and preoperative RT were 45.9% and 48.0%. More than two-thirds of the patients with vertebral primaries received definitive RT. The difference in the distribution of types

Table 2. Patient and treatment characteristics according to local treatment modality

	Definitive RT (n = 266)	Preoperative RT (*n* = 246)	Surgery with or without postoperative RT (*n* = 546)	Surgery without postoperative RT (n = 242)	Surgery with postoperative RT (n = 304)	*p*
CESS 81	44/266 (16.5)	7/246 (2.8)	94/546 (17.2)	50/242 (20.7)	44/304 (14.5)	0.001
CESS 86	111/266 (41.7)	17/246 (6.9)	254/546 (46.5)	92/242 (38.0)	162/304 (53.3)	
EICESS 92	111/266 (41.7)	222/246 (90.2)	198/546 (36.2)	100/242 (41.3)	98/304 (32.2)	
Central tumor location	188/266 (70.7)	118/246 (48.0)	251/546 (45.9)	71/242 (29.3)	180/304 (59.2)	0.001
Proximal extremity	46/266 (17.3)	59/246 (24.0)	138/546 (25.2)	77/242 (31.8)	61/304 (20.1)	
Distal extremity	32/266 (12.0)	69/246 (28.0)	157/546 (28.7)	94/242 (38.8)	63/304 (20.7)	
Pelvis	90/266 (33.8)	66/246 (26.8)	80/546 (14.6)	29/242 (12.0)	51/304 (16.8)	0.001
Vertebra	61/266 (22.9)	8/246 (3.3)	16/546 (2.9)	4/242 (1.7)	12/304 (3.9)	NS
Initial VACA	70/266 (26.3)	28/246 (11.4)	137/546 (25.0)	78/242 (32.2)	59/304 (19.4)	0.001
Initial VAIA	107/266 (40.2)	112/246 (45.5)	272/546 (49.8)	104/242 (43.0)	168/304 (55.3)	
Initial EVAIA	52/266 (19.5)	76/246 (30.9)	80/546 (14.6)	38/242 (15.7)	42/304 (13.8)	
Other	31/266 (11.7)	28/246 (11.4)	43/546 (7.8)	17/242 (7.0)	26/304 (8.6)	
Median follow-up (mo)	120	64	126	120	128	

Abbreviations: RT = radiotherapy; CESS = Cooperative Ewing's Sarcoma Study; EICESS = European Intergroup Ewing's Sarcoma Study; VACA = vincristine, adriamycin, cyclophospharmide, actinomycin D; VAIA = ifosfamide instead of cyclophosphamide; EVAIA = addition of etoposide.

Patients who received surgery as first local therapy modality are further differentiated between those who did or did not receive postoperative radiotherapy.

Numbers in parentheses are percentages.

of local therapy among the trials was statistically significant. Preoperative RT was used in <5% of patients in CESS 81 and 86 and in >40% of patients treated in EICESS 92. Local and combined local and systemic relapses according to local therapy modality and tumor and treatment characteristics are shown in Table 3. After definitive RT, the incidence of local failure, including combined local and systemic relapses, was 26.3%; it was 5.3% after preoperative RT and 7.5% after surgery with or without additional postoperative RT. For the entire study population, the difference in local control among the types of local therapy was statistically significant ($p = 0.001$). Figures 2 through 5 show the competing risk analyses for each local therapy modality. In CESS 81, local control of patients who received definitive RT was inferior to that of subsequent trials. When these CESS 81

Table 3. Local and combined local and systemic relapses according to local therapy modality

	Definitive RT	Preoperative RT	Surgery with or without postoperative RT	Surgery without postoperative RT	Surgery with postoperative RT
CESS 81, CESS 86, EICESS 92	70/266 (26.3)	13/246 (5.3)	41/546 (7.5)	10/242 (4.1)	31/304 (10.2)
CESS 86, EICESS 92	50/222 (22.5)	11/239 (4.6)	29/452 (6.4)	5/192 (2.6)	24/260 (9.2)
Central	44/188 (23.4)	10/118 (8.5)	36/251 (14.3)	6/71 (8.5)	30/180 (16.7)
Proximal	14/46 (30.4)	0/59 (0)	2/138 (1.4)	1/77 (1.3)	1/61 (1.6)
Distal	12/32 (37.5)	3/69 (4.3)	3/157 (1.9)	3/94 (3.1)	0/63 (0)
Tumor volume (cm^3)					
<100	17/93 (18.3)	2/85 (2.4)	12/172 (6.9)	5/82 (6.1)	7/90 (7.8)
≥100	39/137 (28.5)	10/150 (6.7)	21/314 (6.6)	3/133 (2.3)	18/181 (9.9)
Radical resection	—	0/4 (0)	1/68 (1.4)	1/63 (1.6)	0/5 (0)
Wide resection	—	8/165 (4.8)	19/318 (5.9)	6/145 (4.1)	13/173 (7.5)
Marginal resection	—	0/30 (0)	4/70 (5.7)	1/18 (5.6)	3/52 (5.8)
Intralesional resection	—	1/14 (7.1)	11/51 (21.5)	2/7 (28.6)	9/44 (20.5)
Good histologic response after initial chemotherapy	—	—	14/282 (4.9)	3/154 (2)	11/128 (8.6)
Poor histologic response	—	—	11/150 (7.3)	3/46 (6.5)	8/104 (7.7)

Abbreviations as in Table 2.

Numbers in parentheses are percentages.

Patients who received surgery as first local therapy modality are further differentiated in patients who did or did not receive postoperative RT.

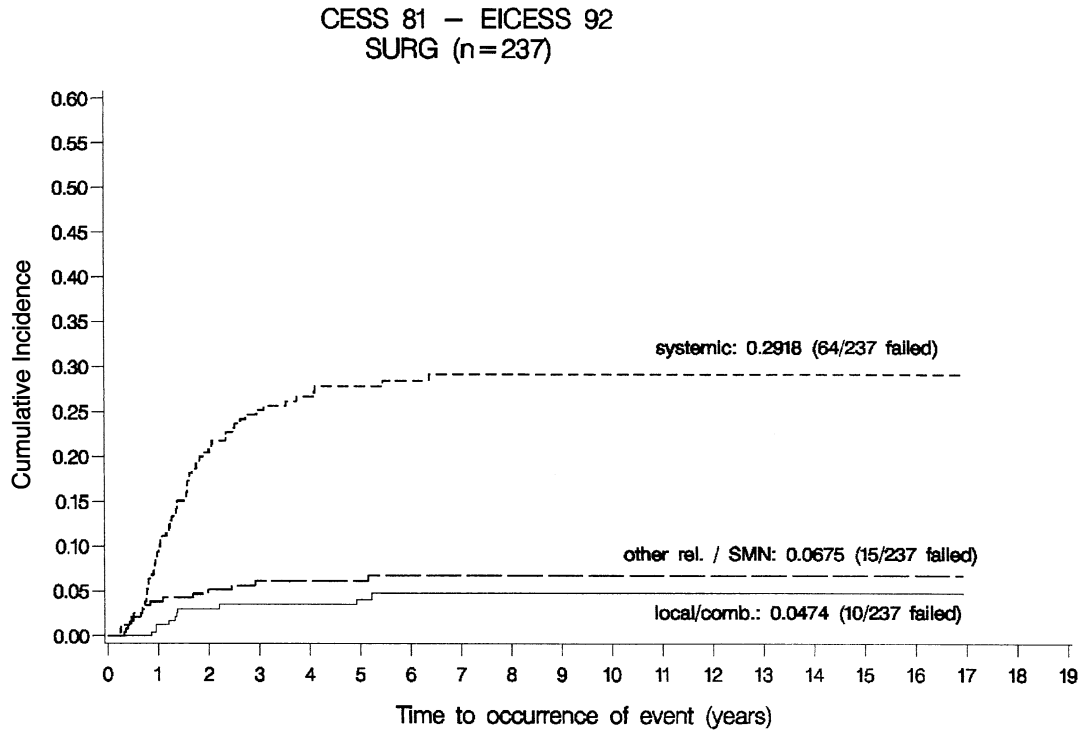

Fig. 2. Competing risk analysis for patients receiving definitive surgery in CESS 81, CESS 86, and EICESS 92. SMN = secondary malignant neoplasm.

patients were excluded, the rate of local and combined local and systemic relapses in patients with definitive RT was still similar (22.5%). The difference in local failure rates among local therapy modalities was also statistically significant after excluding the CESS 81 patients ($p = 0.001$). After preoperative RT, 2 (2.4%) of 85 local

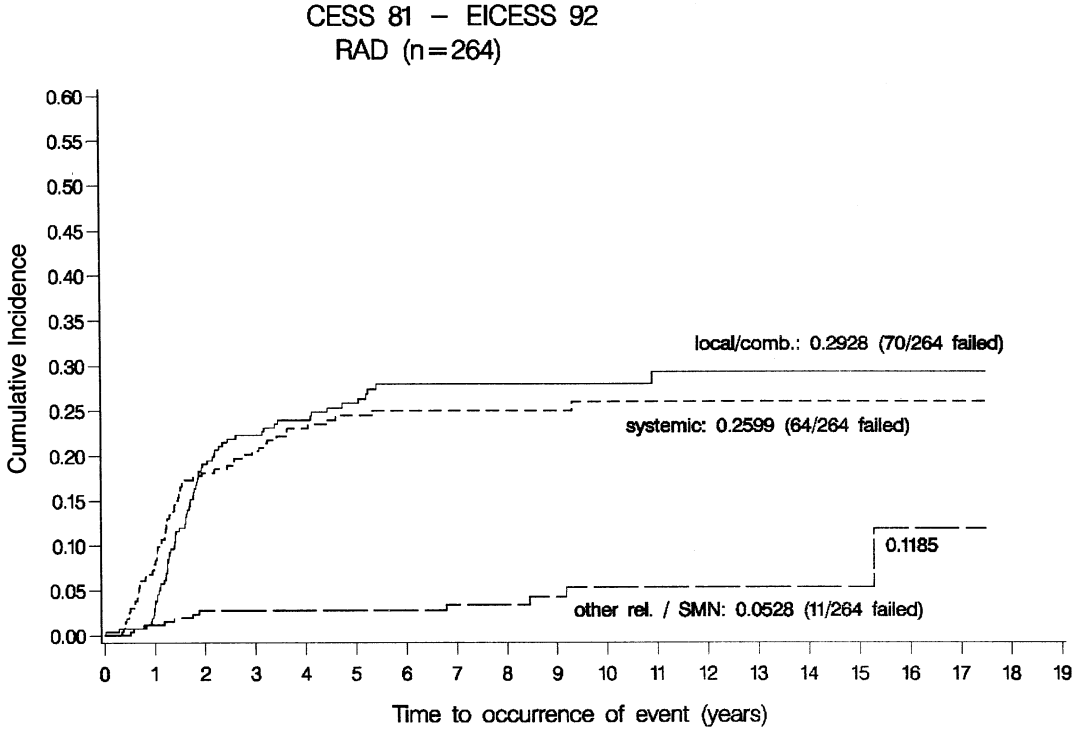

Fig. 3. Competing risk analysis for patients receiving definitive RT in CESS 81, CESS 86, and EICESS 92.

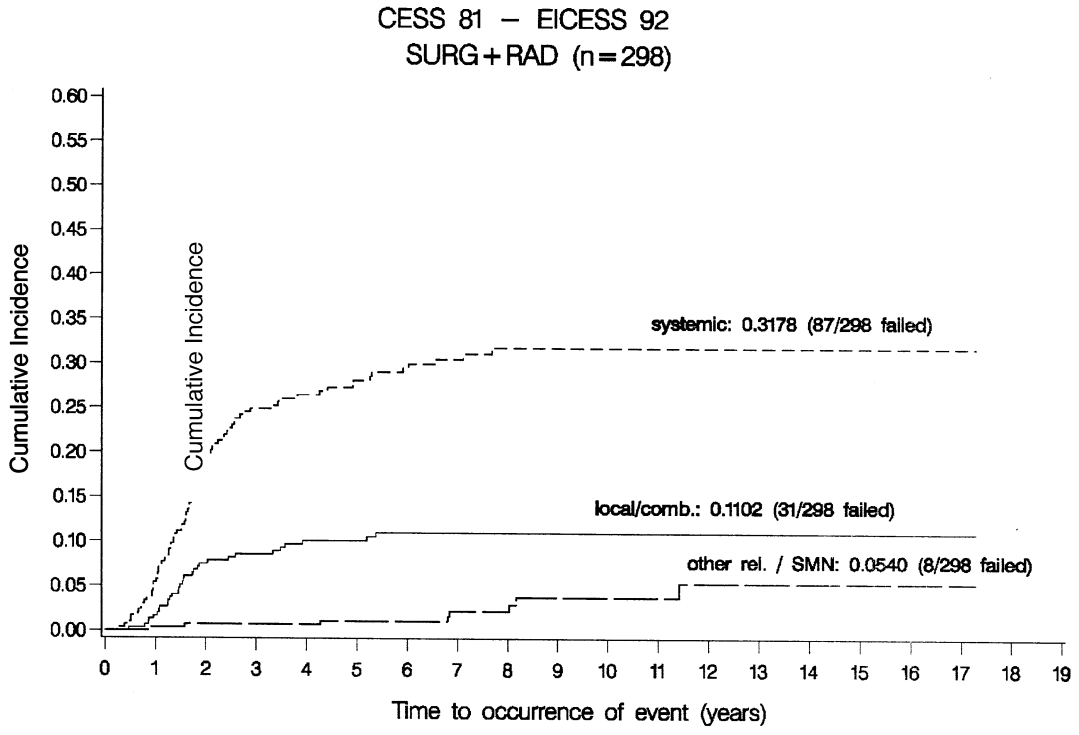

Fig. 4. Competing risk analysis for patients receiving postoperative RT in CESS 81, CESS 86, and EICESS 92.

or combined local and systemic relapses occurred in tumors <100 cm^3 and 10 (6.7%) of 150 in tumors ≥ 100 cm^3 (not significant). The corresponding numbers for central vs. proximal/distal tumor sites were 10 (8.5%) of 118 and 3 (2.3%) of 128 ($p = 0.03$). Of 183 local and combined local and systemic relapses, 41 (23.4%) occurred in patients who received VACA alone, 45 (7.9%) of 567 occurred in patients receiving ifosfamide, and 31

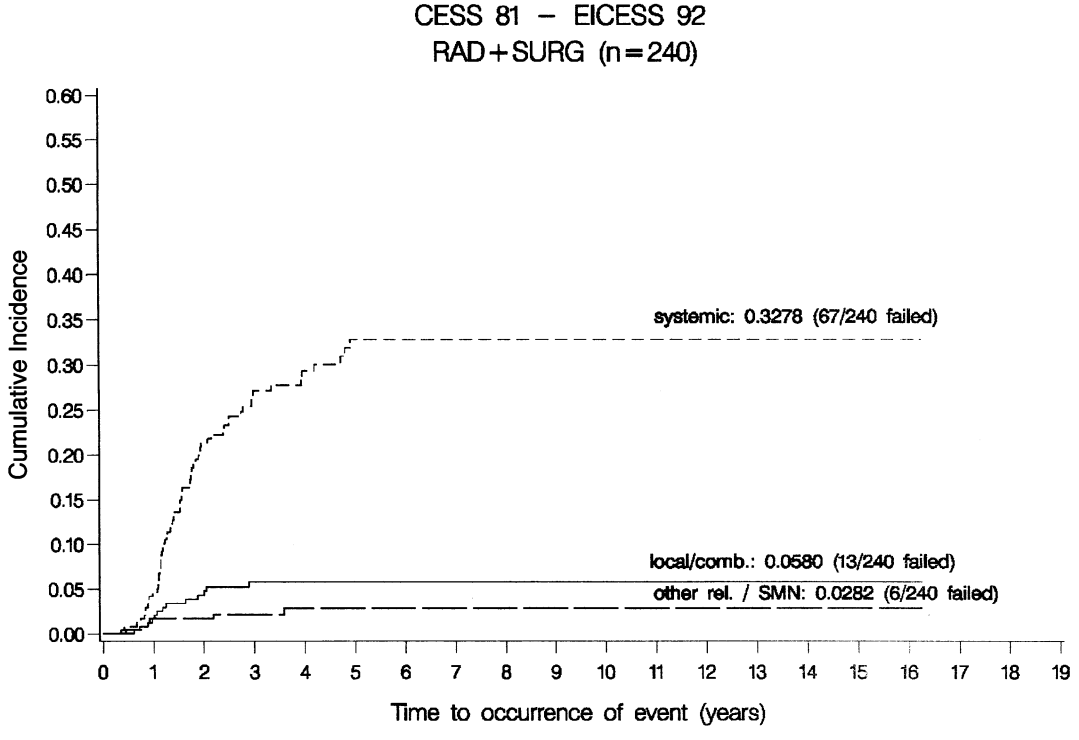

Fig. 5. Competing risk analysis for patients receiving preoperative RT in CESS 81, CESS 86, and EICESS 92.

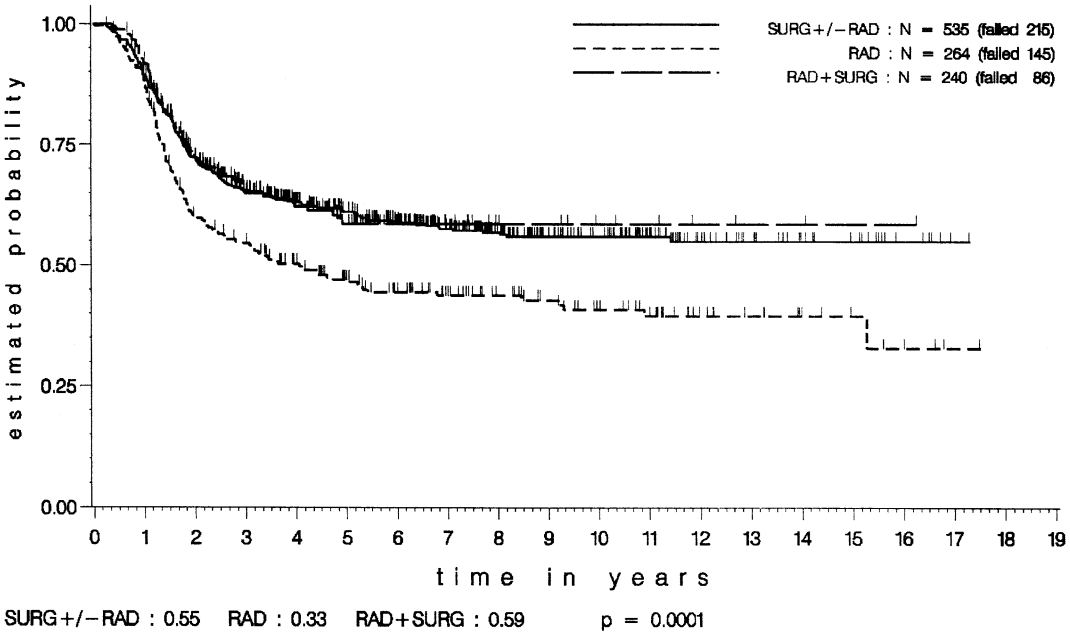

Fig. 6. EFS according to local therapy in CESS 81, CESS 86, and EICESS 92.

(12.3%) of 252 occurred in patients who had ifosfamide and etoposide as part of their treatment ($p = 0.001$). Figure 6 shows the EFS according to local therapy modality in the total group. EFS in patients receiving definitive RT was significantly poorer than in patients who underwent surgery with or without additional RT ($p = 0.0001$). The EFS rate after 5 years in patients receiving definitive RT was 47%; it was 59% after preoperative RT, and 61% after surgery with or without postoperative RT. The corresponding 10-year EFS rates were 40%, 58%, and 55%. The EFS of patients with definitive RT was equivalent to the EFS of those who had intralesional surgery with or without postoperative RT. The corresponding EFS rates after 5 years were 47%, 45%, and 43%. Local failure rates according to selected combinations of tumor or treatment characteristics are shown in Table 4. The histologic response after initial chemotherapy in patients receiving a wide resection according to local therapy is also shown in Table 4. In patients with marginal surgery that was not followed by RT, 13 (72.2%) of 18 patients had a good response. In patients with marginal surgery that was followed by RT, 20 (38.5%) of 52 patients had a good response.

Two secondary malignancies (0.8%) occurred after surgery without additional RT; five secondary malignancies (1.6%), one of which occurred after a metastatic relapse, were recorded after surgery with postoperative RT. One secondary malignancy (0.4%) occurred after

Table 4. Local and combined local and systemic relapses according to combined tumor or treatment characteristics

	Definitive RT	Preoperative RT	Surgery with or without postoperative RT	Surgery without postoperative RT	Surgery with postoperative RT
Extremity tumor (cm^3)					
<100	10/36 (27.7)	1/56 (1.7)	3/110 (2.7)	3/64 (4.6)	0/46 (0)
≥100	11/31 (35.4)	2/67 (2.9)	1/159 (0.6)	0/88 (0)	1/71 (1.4)
Central tumor (cm^3)					
<100	7/57 (12.3)	1/29 (3.4)	9/62 (14.5)	2/18 (11.1)	7/44 (15.9)
≥100	28/106 (26.4)	8/83 (9.6)	20/155 (12.9)	3/45 (6.6)	17/110 (15.4)
Wide resection and good histologic response	—	—	6/190 (3.1)	1/101 (1)	5/89 (5.6)
Wide resection and poor histologic response	—	—	6/84 (7.1)	3/25 (12)	3/59 (5.0)

Abbreviation: RT = radiotherapy.

Patients who received surgery as first local therapy modality are further differentiated in patients who did or did not receive postoperative RT.

preoperative RT; and three secondary malignancies (1.1%) occurred after definitive RT. In the surgery-only group, 1 patient each developed leukemia and a solid tumor; 3 cases of leukemia and 6 solid tumors were reported in those who received RT with or without surgery. No statistically significant difference was found in the incidence of secondary tumors among the different local therapy modalities.

DISCUSSION

The comparison among the local therapy modalities for Ewing tumors in this and all other published analyses is open to considerable bias. The choice of local therapy is influenced by several factors, such as tumor site, tumor size, response to chemotherapy, patient age, and institutional policy (16–19). Although several trials, including those reported here, have addressed randomized study questions, these usually involved the chemotherapy regimen and never the choice of local therapy. Because of the multitude of factors influencing the choice of local treatment, a randomization of local therapy for Ewing tumors is not likely to be addressed in the near future. Nevertheless, physicians, including pediatricians and radiation oncologists, are faced with the task of selecting the most appropriate local therapy for each new patient. To find a suitable strategy, nonrandomized series have to be evaluated, even in view of the above-mentioned biases. Reports in the literature about this topic have been controversial. Several authors have reported that local control and survival with surgical local treatment were superior to definitive RT (16, 20–23). In the IESS-II study for nonpelvic lesions, no difference in survival was reported in patients who did or did not receive RT (8). The local control rate was not reported. We analyzed the data of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials for nonmetastatic Ewing tumors. This is the largest available database on Ewing tumors. The interpretation of the data focused on two main questions: what is the role of definitive RT, and when is combined local therapy indicated?

Role of definitive RT

Local control in patients who received definitive RT was significantly inferior to that in patients undergoing surgery with or without additional RT. There were 26.3% local and combined local and systemic relapses in the CESS and EICESS trials after definitive RT compared with 5.3% after preoperative RT and 7.5% after surgery with or without postoperative RT. These results are reflected in the EFS. Patients who received definitive RT had a significantly reduced EFS compared with all other local therapy groups (Fig. 6). Patients receiving RT alone, however, represented a negatively selected subgroup of the study population and cannot be directly compared with patients who received surgery (Table 2). Vertebral lesions that are difficult to treat with a sufficient radiation dose because of the proximity of the spinal cord are overrepresented in the subgroup of patients with definitive RT, and the proportion of limb tumors, which could be approached much more easily, is comparatively low. Regarding tumor volume, no statistically significant difference was found in distribution. The question still remains to what extent the observed improved local control rate in surgical patients is a reflection of the selection bias. Unfavorable results with definite RT would be expected in patients with large primaries and tumors in the proximity of radiosensitive structures. The latter is mainly the case with central tumor sites. Patients with large primaries ($\geq$100 cm^3) had poorer local control after definitive RT than did patients with small primaries ($<$100 cm^3). The local and combined local and systemic failure rate was 28.5% and 18.3%, respectively ($p = 0.07$). On the other hand, the rate of local or combined failure was 2–8% in patients who underwent surgery with or without additional RT and had small primaries (Table 3). Hence, tumor size alone cannot be the only determinant of local control in irradiated patients compared with surgical patients. The same holds true for the impact of tumor site. Definitive RT was associated with more local failures than other local therapy modalities in central, as well as peripheral, sites (Table 3). In tumors combining the theoretically favorable features of "small initial tumor size" and "tumor of the extremity," 2.7% local relapses occurred after surgery with or without postoperative RT, 27.7% occurred after definitive RT, and 1.7% after preoperative RT. Surgery with or without additional RT thus achieves superior local control rates compared with definitive RT in this favorable subgroup. In patients with central tumors $<$100 cm^3, definitive RT achieved good results with a 12.3% rate of local failure—a local failure rate comparable to that of patients who underwent resection (Table 4).

After intralesional resection, 2 of 7 patients had a local relapse after surgery without additional RT (28.6%). In patients who received postoperative RT after intralesional resection, the incidence of local or combined failure was reduced (20.5%, Table 3). Despite the small patient numbers, we consider postoperative RT to be indicated after intralesional resection. The incidence of local failure after definitive RT was 26.3% in the entire study population and 22.5% when the CESS 81 patients were excluded. These results are comparable with the treatment results obtained with postoperative RT after intralesional resection. Furthermore, the EFS in patients who received definitive RT was equivalent to that of patients who underwent intralesional resection with or without postoperative RT. The observations confirm that intralesional resection or debulking procedures followed by postoperative RT do not offer increased local control or survival compared with RT alone and should be avoided. Fourteen patients underwent intralesional resection after RT. Only 1 of these patients had local failure. This good local control rate may have been due to the small patient numbers or a selection bias. However, local control might be improved by resecting residual tumor after RT even with narrow resection margins.

Role of combined surgery and RT

The CESS and EICESS trials favored the use of combined modalities for local therapy. Postoperative RT was performed in CESS 81 when residual tumor-bearing bone remained *in situ* and in CESS 86 and EICESS 92 when intralesional or marginal resections were performed or when a poor histologic response to preoperative chemotherapy was found in the surgical specimen. The risk of local and combined local and systemic relapses after 5 years in these patients was 10% (Fig. 4). The main criteria for the application of postoperative RT were the resection status and histologic tumor response. As mentioned above, those few patients who underwent intralesional surgery had poor local control rates and were likely to benefit from postoperative RT. After wide resection, 6 (4.1%) of 145 patients with surgery alone and 13 (7.5%) of 173 patients with surgery plus postoperative RT had local or combined local and systemic failure (Table 3). When these numbers were differentiated further according to the histologic response status, patients with surgery and no additional RT, wide resection and a good histologic response did well, with 1 (1%) of 101 local and combined relapses (Table 4). Those patients, however, who matched for treatment but had a poor histologic response failed locally in 3 (12%) of 25 cases. Patients with postoperative RT after wide resection showed no difference in local failure according to histologic response. Good responders had a 5.6% rate of local or combined failure, poor responders 5.0%. Local control was thus superior in patients with wide resection and a poor histologic response who received postoperative RT compared with those who did not. It can be concluded that postoperative RT in poor responders after wide resection improves local control and is justified.

Marginal resection without additional RT was associated with local failure in 1 (5.6%) of 18 patients, 13 of those patients had a good histologic response (72.2%). Three (5.8%) of 52 patients had local failure after marginal resection plus postoperative RT, but only 20 of those patients (38.5%) had a good histologic response. Even though patients who received postoperative RT were negatively selected concerning histologic response, local control was equivalent in marginally resected patients who did or did not undergo postoperative RT.

In the EICESS 92 trial, a high proportion of patients was treated with preoperative RT (41.8%). Although EFS was not improved in patients who received preoperative RT compared with those who underwent surgery with or without postoperative RT (Fig. 6), local control was excellent in this subgroup. The competing risk analysis showed a local and combined local and systemic failure rate of 6% after 5 years (Fig. 5). An initial tumor size <100 cm^3 (not significant) and extremity site ($p = 0.03$) were associated with better local control. As shown in Table 4, the type of surgery after preoperative RT seemed to have little impact on the local failure rate. If function-preserving surgery with narrow resection margins is anticipated, the application of preoperative RT may thus be helpful to raise the local control rate.

Secondary tumors occurred in 1.0% of the patients. The incidence of secondary malignancies revealed no statistically significant difference among the local therapy modalities. The follow-up, however, was too short to evaluate this aspect fully.

CONCLUSION

When marginal or wide resections are feasible, tumor resection should be done. Postoperative RT is advisable in the case of wide resection with a poor histologic response and after marginal or intralesional resection, irrespective of the histologic response. After intralesional resection, the results in patients receiving postoperative RT were comparable with those achieved by definitive RT. Initial intralesional resections or debulking procedures should thus be avoided and RT given instead, possibly followed by tumor resection. Very good local control could be achieved in patients who received preoperative RT, although the EFS was not improved in this subgroup.

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REVIEW
Post-Operative Radiotherapy for Ewing Sarcoma: When, How and How Much?

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Postoperative radiotherapy in Ewing family of tumors has undergone continuous evolution over the last few decades to establish its role in the combined modality management of these tumors. The process of evolution is still far from over. This review analyzes the evidence from major multi-institutional prospective trials as well as large retrospective institutional series in Ewing tumors to determine the current standards and controversies in postoperative radiation. The indications of PORT, radiation dose-fractionation, timing, target volumes and treatment planning, as well as the late effects are reviewed. A summary of evidence based consensus is presented and unresolved aspects are discussed. Pediatr Blood Cancer 2008;51:575–580. © 2008 Wiley-Liss, Inc.

Key words: Ewing/PNET; histopathological response; radiation therapy; surgery

INTRODUCTION

Local control is of immense importance in Ewing family of tumors (EFT). Even though systemic failures are very common, the evolution of treatment in EFT through cooperative trials and large institutional series demonstrates that improvement in local control has been the major route to improved outcomes. Data from the Cooperative Ewing Sarcoma Study (CESS) 81, CESS 86 and European Intergroup Cooperative Ewing Sarcoma Study (EICESS) 92 trials demonstrate that the improvement in event-free survival from 54% to 62% is paralleled by the reduction in local or combined failures from 26% to 9%, even at the cost of a higher relative incidence of distant metastasis [1,2]. The more frequent use of surgery has been one of the major reasons for improved local control. However, in a significant proportion of patients, especially with axial primaries or large residual tumors after induction chemotherapy, the risk of local or combined failures is high after surgery alone because wide excision is difficult to achieve. The addition of post-operative radiotherapy (PORT) in these patients has resulted in improved rates of local control and event-free survival. These improved control rates now result in equivalent survival for patients with tumors at unfavorable sites (e.g., the pelvis) compared to the entire cohort of patients in the CESS and EICESS studies [2].

Despite the significance of PORT in the current management of EFT, there are a number of issues that are unresolved with current evidence. These include patient selection, dose-fractionation, timing of RT and the choice of radiation target volumes. This review highlights some of these uncertainties and analyzes the published literature for evidence to resolve these issues.

INDICATIONS FOR POST-OPERATIVE RADIATION

Surgical Margins

Surgical resection has traditionally been described according to the Enneking classification (Table I). Radical or wide resections are usually considered 'adequate' surgery, while marginal or intralesional resections are termed 'inadequate' surgery. PORT has been traditionally administered for intralesional and marginal resections.

Several investigators have reported on the prognostic importance of surgical margins (Table II). The adequacy of surgical margins seems to have a clear impact on treatment outcomes. It is important to note that these results have been obtained even after radiation has been added to surgery in the majority of patients with positive or close margins.

How much benefit in local control does RT provide after marginal resection? What is the extent by which PORT decreases the incidence of local failure after marginal resection? Ozaki et al. [4] noted a local failure rate of 12% versus 14% without RT. Bacci et al. [5] noted a 16% absolute benefit in EFS with RT after inadequate surgery but it was not statistically significant. In the combined analysis of RT in the CESS and EICESS trials, the rates of local failure for marginal resection with or without RT were 5.8% and 5.6% respectively [8].

This apparent lack of significant benefit must be put in context. Since RT is usually indicated after marginal resections in most institutional or cooperative protocols, those not receiving PORT usually have favorable disease characteristics. In the analysis by Schuck et al., [8] a much higher proportion of patients receiving RT had a poor histological response. Despite this, the two groups show equivalent local control. Can RT be omitted then in marginal resections if there has been a good histopathological response to chemotherapy? There is no direct evidence to suggest that surgical margins have a lesser impact in good responders. In the analysis by Bacci et al. [5] the poor local control after inadequate surgical margins were irrespective of the histological response. Local failure rates were 13% versus 5% ($P = 0.005$) among good responders and 22% versus 14% ($P = 0.55$) among poor responders depending on whether the margins were inadequate or adequate.

What is the role of RT after intralesional resection? RT administered after intralesional resection reduces the chances of local failure. In an analysis of CESS and EICESS data, the local failure rate was reduced from 28.6% to 20.5% with RT after intralesional resections [8]. However, the outcomes after surgery and PORT were similar to control rates with RT alone. There is, therefore, little role for debulking surgery in EFT.

Current consensus favors the use of PORT in all patients with marginal or intralesional resection. Current Children's Oncology Group (COG) protocols have more specifically defined adequate margin status. Complete resection is defined as a minimum of 1 cm margin and ideally 2–5 cm around the involved bone. The minimum

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TABLE I. Enneking Classification of Surgical Intervention [3]

Intralesional resection	Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease
Marginal resection	Tumor removed en bloc; however, resection through the pseudo-capsule of the tumor; microscopic residual disease likely
Wide resection	Tumor and its pseudo-capsule removed en bloc, surrounded by healthy tissue, within the tumor bearing compartment
Radical resection	The whole tumor-bearing compartment removed en bloc

soft tissue margin for fat or muscle planes is at least 5 mm and for fascial planes at least 2 mm [9].

Histopathological Response to Chemotherapy

The importance of histological response to chemotherapy as a prognostic factor for outcome has been recognized for some time. Several authors have reported a clear impact of histologic response on event-free survival, local control, and overall survival (Table III).

Does histopathological response predict for locoregional control? The predominant mode of failure in poor histologic responders has been systemic. In the series by Picci et al. [10] none of the poor responders to chemotherapy had an isolated local failure. However, Lin et al. [7] found histological response an independent prognostic factor for local control in a multivariate analysis. Wunder et al. [11] have also reported more local recurrences in poor responders. Thus, the addition of RT may improve local control and positively impact event-free and overall survival in poor responders to chemotherapy (Table IV).

Does PORT actually benefit patients with poor response to chemotherapy? The incorporation of histological response to chemotherapy as an indication for PORT has been a gradual process over the past two decades. The EICESS 92 was perhaps the first cooperative group trial to include poor histologic response (<90% necrosis) as an indication for PORT even with clear surgical margins. In their analysis there was reduction in local failures (5% vs. 12%) in the poor responders if they received PORT [8]. The impact of this benefit on overall survival is not yet clear, but it seems rational to incorporate histopathological response to chemotherapy in the decision making process on PORT.

What is the best threshold for necrosis rates in the addition of PORT? The best threshold for the extent of necrosis for the addition of PORT is yet unknown. According to the CESS and EICESS results the local control rates with more than 90% necrosis seem low enough for omitting RT [8]. Wunder et al. [11] found no difference in outcomes between those who had 90–99% necrosis and those with 100% necrosis. In contrast, analyses by Elomaa et al. [12], Oberlin et al. [14] and Lin et al. [7] (Table II) seem to show that there is scope for improvement in those with necrosis up to 95% or 99%. Until a consensus emerges, most institutions will follow their own practice in choosing the threshold.

Other Indications of PORT

In the CESS and EICESS trials, the local failure rate for central primaries was reduced by ~50% with PORT [8]. Lin et al. [7] also found an independent prognostic relevance for tumor site with PORT. However, the potential advantage of using PORT in all central primary disease sites must be weighed against the long term effects of RT to the pelvis or chest wall.

Dose-Fractionation

The total dose of radiation in PORT depends on the extent of resection, the margin status as well as the histological response to chemotherapy. Most current protocols have a fairly uniform dose prescription. For tumors with intralesional resection doses equivalent to radical radiotherapy (55–60 Gy) are delivered. For microscopic residual disease, the usual delivered dose is between 45 and 50 Gy. When radiation is added after surgery with clear margins based on a poor histological response to chemotherapy, the

TABLE II. A Comparison of Outcomes Based on Surgical Margins

References	Margins	Local control	Event-free survival	Overall survival
Ozaki et al. [4]	Adequate	96%		
	Inadequate	88%		
		($P = 0.045$)		
Bacci et al. [5]	Adequate	93%	69.5%	
	Inadequate	81%	50% ($P < 0.001$)	
		($P = 0.001$)		
Sluga et al. [6]	Adequate			60.2%
	Inadequate			40.1% ($P < 0.05$)
Lin et al. [7]	≥10 mm	93%		
	3–9 mm	83%		
	≤2 mm	78%		
		($P = 0.23$)		

TABLE III. Studies Reporting the Prognostic Importance of Histopathological Response to Neo-Adjuvant Chemotherapy

References	Response criteria	EFS/DFS	OS	LC
Picci et al. [10]	Extremity tumors only			
	Grade I (macroscopic visible tumor)	34%		
	Grade II (microscopic viable tumor)	68%		
	Grade III (no viable tumor cells)	95%		
Wunder et al. [11]	Necrosis			
	≤50%	19%		
	>50% to <90%	22%		
	90–100%	59%		
Elomaa et al. [12]	Necrosis			
	≤50%		0%	
	>50% to <90%		∼55%	
	90–99%		∼60%	
	100%		95%	
Sluga et al. [13]	Salzer Kuntschik criteria			
	Grade 4–6	51.3%	41.7%	
	Grade 1–3	68.8%	80.2%	
Oberlin et al. [14]	Necrosis			
	<70%	20%		
	70–95%	48%		
	>95%	75%		
Lin et al. [7]	Necrosis			
	<90%			51%
	90–99%			75%
	>99%			91%

usual dose is 45 Gy. These doses are most commonly delivered as single daily fractions of 1.8 Gy, though some institutions practice hyperfractionated radiotherapy in a significant proportion of their patients [15,16]. Anatomic considerations may result in dose modifications, although doses to the spinal cord, heart and liver must be kept within tolerance. Despite this apparent consensus, several issues remain unresolved.

Does a poor histological response with microscopic margins merit a higher dose? Donaldson recommends a further boost of 10 Gy when tumors with microscopic positive margins also show a poor response to chemotherapy, making the total dose in these tumors equivalent to the dose for gross disease, probably due to the fact that local failures are higher for this subgroup despite the addition of RT at standard doses [9]. However, no clear dose-response relationship has been demonstrated in EFT for doses above 40 Gy. Also, in the CESS and EICESS studies, a dose of 45 Gy for post-operative cases with marginal resection and/or poor histological response demonstrated excellent local control, with local failure rates of only 5%.

Are lower radiation doses for selected patients an acceptable alternative? Results with low-dose radiation have been reported in radical and adjuvant settings with the intention of reducing long term sequelae while testing its efficacy in local disease control. Merchant et al. have reported a series of patients from Memorial Sloan-Kettering Cancer Center (MSKCC) treated with low dose RT (30–36 Gy) following limited surgery and demonstrated no local failures [17]. Rosen et al. [18] reported outcomes on patients treated with surgery and PORT with 30 Gy and reported satisfactory local control and a trend towards an overall survival benefit over surgery alone. A subset of patients in the CESS 81 trial also received low dose RT 36 Gy after inadequate resection with acceptable results [19]. In contrast, Krasin et al. [20] reported a trend towards inferior outcomes with PORT doses of <40 Gy in patients treated at St. Jude Children's Research Hospital (SJCRH). The rates of local failure with doses <40 Gy was $15.5 \pm 7\%$ versus $0 \pm 0\%$ with higher doses.

Currently used adjuvant RT doses of 45 Gy result in excellent rates of local control (>90%) with only a small risk of severe late

TABLE IV. Summary of Recommendations on Post-Operative RT

Indications	Gross or microscopic positive margins
	Clear margins but poor histopathological response to chemotherapy (necrosis <90% is the suggested minimum threshold, but <95–99% may be used based on institutional practice)
Timing	Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)
Dose	45 Gy to the pre-chemotherapy volume
	10.8 Gy boost to areas of gross tumor residual
Fractionation	Standard daily fractionation of 1.8 Gy per fraction
	Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects
Target volume	Initial phase (45 Gy): pre-chemotherapy tumor volume on MRI with 1.5–2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung
	Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins

toxicity. Unless lower RT doses show local control rates that are unequivocally at par with these results, this dose may be considered the standard safe and effective dose in the post-operative setting.

What is the role of hyperfractionated RT? In the CESS 86 trial, hyperfractionated split-course irradiation was compared with conventionally fractionated RT with the same total dose and overall treatment time, but without a significant improvement in the 5-year outcomes [21]. More recently, preliminary results from the Italian Co-operative SE-91-CNR protocol using hyperfractionated accelerated RT appear promising with a low incidence of local failure of only 6% at 3 years [22].

Yet, hyperfractionated RT (with lower doses per fraction) has the potential to reduce long term musculoskeletal side effects while maintaining similar control rates. An analysis of patients treated at the University of Florida with hyperfractionated (twice daily 1.2 Gy) or conventionally fractionated RT reveals that while local control rates are similar, the patients treated with hyperfractionated RT had significantly lower rates of pathological fracture, loss in range of motion and muscle atrophy than those who were conventionally irradiated [16,23]. The role of hyperfractionation as a tool for improving local control may be in question, but it may be an option individual institutions may adopt in order to reduce the long term sequelae.

Timing of Post-Operative Radiation

The timing of radiation after surgery is still an issue to be resolved. In an analysis of patients receiving PORT in the CESS 86 and EICESS trials, Schuck et al. [24] reported no significant difference in the local control and survival of patients who received RT within 60 days of surgery or later. This is in contrast to the improved local control in CESS 86 over CESS 81 when the timing of RT was brought forward from the 18th week to the 10th week [1]. Though there were other factors (including centralized radiation review and more intensive chemotherapy) that contributed to improved local control, it would be unadvisable to delay local treatment if it is to provide the maximum possible benefit.

Target Volumes and Radiation Treatment Planning

Target volumes for radiation in EFT have conclusively reduced from the traditional practice of whole bone RT to localized portals. The (Pediatric Oncology Group) POG #8346 trial demonstrated no difference in outcomes between patients randomized to whole bone radiation plus a localized boost or involved field radiation alone [25]. The target volume for involved field radiation was the initial pre-chemotherapy volume on CT scans or MRI with a 2 cm margin. The majority of local failures were well within the radiation portals. A study from SJCRH evaluating limited volume irradiation also noted that the majority of local failures occurred centrally within the irradiated area [26].

Do these principles of radical intent radiation apply unchanged for PORT? Is it necessary to treat the entire pre-chemotherapy or even preoperative volume if only a specific small area has a microscopic positive margin? If radiation is indicated for poor histopathological response to an otherwise widely resected tumor, what is the optimal margin that is required? Unfortunately there is no high level evidence to address these issues adequately. The majority of co-operative trials have treated the pre-chemotherapy volume to a dose of 45 Gy before reducing the fields to boost the operative bed with margins if indicated.

In the absence of standard guidelines, the pre-chemotherapy volume on MRI should be treated with a 1.5–2 cm margin to a dose of 45 Gy. For tumors with clear or microscopic margins no further RT is indicated. If there is a gross residual disease as in the case of an intralesional resection, the residual tumor site will be additionally boosted to radical doses with a similar margin.

Initial volumes should be reduced in those tumors protruding into cavities or the lung in order to reduce normal tissue irradiation. The post-chemotherapy status within the cavity or lung should be covered with margins adequate to account for patient movement and organ motion (e.g., respiratory motion). Care should be taken to avoid treating the entire circumference of extremity or the epiphysis of adjacent growing bones. The surgical scar should be entirely covered whenever feasible [9].

The importance of quality control and centralized review for radiation treatment planning in EFT needs special emphasis. The inferior local control rates in the CESS 81 trial were attributed to a great extent to suboptimal radiation treatment, and improved dramatically in the CESS 86 study when rigorous quality checks and centralized review was incorporated in the radiation treatment planning process [1]. In the POG #8346 study, analysis showed that patients treated appropriately with RT had a high local control of 80% which reduced to 48% with minor deviations and 16% with major deviations [25]. With the routine use of limited portals, it is now strongly advocated that appropriate evaluation of MRI and CT scans, preferably by a musculoskeletal radiologist, be used for radiation treatment planning.

The role of intensity modulated radiotherapy (IMRT) and proton beam therapy is being investigated in the management of bone and soft-tissue tumors, including EFT [27]. These techniques offer the potential to deliver higher doses to the tumor bed, while sparing adjacent critical organs. EFT of the pelvis, vertebrae and chest wall are ideal candidates for these new techniques, where adequate doses are difficult to deliver without risking normal tissue toxicity. At other sites conformal radiation allows a greater sparing of normal tissues, reducing the risk of long term morbidity.

Side-Effects of Post-Operative Radiation

Does PORT increase the chances of failure of flaps and prostheses? PORT is frequently used in the presence of flap reconstruction in bone and soft-tissue sarcomas. In an institutional experience from MSKCC 95% of flap reconstructions remain viable after RT for extremity sarcomas [28]. The effect of RT on the viability of endoprostheses is a subject of debate. A higher incidence of infections following radiotherapy in the setting of massive endoprostheses has been reported [29]. However, complications following endoprosthetic replacements may be common at certain sites even without adjuvant radiation, especially the distal femur, proximal tibia and the pelvis [30–32]. Given the benefits of radiation in local control, it may not be prudent to withhold RT simply due to the risk of complications.

What is the incidence of late bone and soft-tissue effects of PORT? Only a few reports have described in detail the incidence of delayed bone and soft-tissue effects following radiation for EFT. Paulino reported that while the majority of children with >10 year follow-up had grade I/II toxicity according to the LENT-SOMA

scales for bone growth, atrophy, mobility, fibrosis and edema, a significant proportion required surgical intervention for fractures and limb defects [33]. There was a 39% incidence of serious orthopedic complications in the follow-up of the POG #8346 trial [25]. The incidence in the adjuvant setting is not fully clear, as only moderate radiation doses are usually required and the surgical intervention may have its own sequelae. The use of conformal radiation techniques, that irradiate lesser volumes of normal tissue, may reduce the incidence of these late complications.

What is the incidence of second malignancies after radiotherapy? Several authors have evaluated the incidence of second malignancies after treatment of EFT [34–39]. The incidence has been in the range of 2–10% in these reports. While 50–60% of these have been sarcomas induced by RT, the remaining were hematological malignancies, mainly acute myeloid leukemia and myelodysplastic syndromes, induced by chemotherapy. In a radiation dose-dependency analysis from a multi-institutional database of patients with EFT, Kuttesch et al. [37] found no second cancers among patients receiving less than 48 Gy. Most of the patients receiving PORT receive doses of about 45 Gy that may be safe from this viewpoint. Moreover, in the CESS experience, most secondary bone sarcomas could be easily resected and did not contribute to mortality [35].

CONCLUSIONS

This review of current literature on PORT for EFT suggests that radiation remains an important component its multimodality management. It improves local control in patients with poor risk factors. Improved radiation therapy techniques and lowered radiation doses has resulted in improved outcome and reduced acute and late sequelae. Future studies need to be directed towards selecting patients for whom radiation therapy could be safely avoided and also to further refine RT techniques for achieving a superior therapeutic ratio.

ABBREVIATIONS

CESS	Cooperative Ewing Sarcoma Study (German Society of Pediatric Oncology)
COG	Children's Oncology Group (North America)
EICESS	European Intergroup Cooperative Ewing Sarcoma Study (Europe)
MSKCC	Memorial Sloan-Kettering Cancer Center (New York, USA)
POG	Pediatric Oncology Group (North America)
SJCRHSt	Jude Children's Research Hospital (Memphis, USA)

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International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours

Euro Ewing 2012

EE2012 PROTOCOL RADIOTHERAPY GUIDELINES

All cases should have local therapy discussed within specialist multidisciplinary team (MDT) meetings. The MDT should include medical/paediatric oncologists, surgeons and radiation/clinical oncologists. All UK patients should be discussed at the UK National Ewing's MDT. French patients will be discussed in the paediatric radiotherapy web-conferencing meeting. Early discussion is strongly encouraged, ideally with first discussions at diagnosis, to allow optimal planning of local therapy.

Surgery should be considered as local therapy whenever feasible, as there is evidence that it is superior to radiotherapy alone as definitive local therapy. Radiotherapy is used as definitive local therapy in inoperable tumours, or in combination with surgery either pre- or postoperatively. These guidelines include discussion of the use of post-operative radiotherapy after intra-lesional surgery with residual microscopic disease (R1 excision). However, it should be noted that if surgery is planned carefully within a multidisciplinary team (MDT), and is carried out by experienced surgeons, this should be an unusual occurrence. Debulking procedures leaving macroscopic residual disease (R2 excision) should not be performed, although this may have occurred if a patient has had surgery for an unsuspected diagnosis, e.g. debulking surgery for spinal cord compression caused by a spinal tumour.

1. Indications for radiotherapy

Radiotherapy may be given to the primary tumour preoperatively, postoperatively or as definitive local therapy:

1.1. Pre-operative radiotherapy

Indications for planned preoperative radiotherapy include expected marginal resections, or if radiotherapy is anticipated to be required for another indication and it is judged at MDT discussion for there to be a technical advantage to giving radiotherapy prior to surgery.

1.2. Postoperative radiotherapy

Postoperative radiotherapy is considered for *all* patients *except* for:

- those who have had a wide local excision, defined as negative resection margins of at least 1mm;
- *and* a good histological response (>90% necrosis) to pre-operative chemotherapy;
- *and* with removal of all tissues originally involved by the pre-chemotherapy tumour volume;
- *or* for those in whom the anticipated adverse side effects of radiotherapy are sufficiently high to outweigh the additional benefit of radiotherapy for local control (anticipated to be an improvement of approximately 10%) for an individual patient. Reasons for deciding against radiotherapy may include:
    - Concerns about impaired wound healing following surgery and radiotherapy
    - Concerns about morbidity of giving radiotherapy to young patients
    - Concerns about the increased risk of infection of a metallic prosthesis following radiotherapy
    - Concerns about the risk of a 2nd radiation-induced malignancy

Specific indications *for* post-operative radiotherapy include:

- For positive surgical margins with microscopic residual disease (R1 excision; <1mm or tumour up to edge of resection specimen) if further surgery to achieve negative margins is not possible
- For positive surgical margins with macroscopic residual disease (R2 excision), if further surgery to achieve negative margins is not possible (this should be an unusual situation)
- For negative surgical margins if all tissues involved by the original pre-chemotherapy tumour volume have not been excised
- For negative surgical margins if poor histological response (≤ 90% necrosis) to pre-operative chemotherapy
- Displaced pathological fracture of bone at primary site (unless it is possible to excise all contaminated tissue)
- For certain tumour sites, where local control is judged to be more difficult to achieve:
    - Spine and paraspinal sites - because in these sites excision is rarely complete, and is often intra-lesional
    - Pelvis and sacrum – because in these sites it is frequently difficult or impossible to be sure that the entire pre-chemotherapy tumour volume has been excised
    - Rib tumours when presenting with a pleural effusion

1.3. Definitive radiotherapy

Definitive radiotherapy is advised only in inoperable lesions. Inoperability is decided following MDT discussion, for tumours that cannot be resected completely, and in tumour sites where complete surgery would result in unacceptable morbidity or would be associated with a high risk of significant complications.

1.4. Whole lung radiotherapy

Whole lung radiotherapy is indicated in patients with pulmonary or pleural metastatic disease (R2 VAI and R2 IEVC) in both arms A and B.

2. Timing of radiotherapy

2.1. Radiotherapy to primary tumour

Surgery is scheduled to occur after 6 cycles of VIDE chemotherapy for arm A (i.e. week 18) or 9 cycles of VDC/IE for arm B (i.e. week 18). Radiotherapy can be given either prior to or after surgery, or as definitive local therapy, at this time. Early MDT discussions regarding local therapy, ideally after the first response evaluation, are strongly encouraged.

Patients who are to receive postoperative radiotherapy following surgery should continue with chemotherapy to allow recovery from surgery, wound healing and planning of radiotherapy. Radiotherapy should be aimed to start during the 2nd to 4th cycles of post-operative consolidation chemotherapy. Delays in starting RT should be avoided. Actinomycin D (arm A) or doxorubicin (arm B) should to be omitted during radiotherapy, and re-introduced after completion of radiotherapy after acute reactions have resolved (see section 7). For patients who have had a biological reconstruction as part of their surgery, it may be desirable to delay post-operative radiotherapy in order to allow time for the bone graft to unite.

For R2 VAI and R2 IEVC patients with pulmonary and/or pleural metastatic disease, whole lung radiotherapy is given on completion of consolidation chemotherapy.

3. Radiotherapy techniques and delivery

Patients will be treated with CT-planned conformal 3D radiotherapy using dose volume histograms to assess doses to organs at risk. Intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or tomotherapy can be used at centres with access to this technique, and should be particularly considered for head and neck, pelvic and paraspinal tumours in order to achieve optimal dose distributions and dose delivery. Proton beam radiotherapy is also permitted as long as this does not compromise delivery of chemotherapy. Patients should be immobilised using customised immobilisation devices for limb, and head

and neck, tumours. Image guided radiotherapy (IGRT) should be used, according to institutional protocols. Dose specification is according to the ICRU 50 and 62 reports.

4. Target volume definition

Target volumes are defined in accordance with ICRU 50 and 62. The principle of treatment is to treat tissues originally involved by tumour at initial diagnosis prior to chemotherapy. A shrinking volume technique may be used in some situations following surgery, with a phase I to include the tumour and involved tissues, and scars and prosthesis; and a smaller phase II to include the tumour and involved tissues only. **N.B. Please also see site-specific guidelines in section 6.**

4.1. Pre-operative and definitive radiotherapy

4.1.1. Gross tumour volume (GTV)

GTV is defined as the visible tumour on imaging at its maximal extent (using CT, PET, bone and MRI scans, as available) prior to any chemotherapy or surgery. MRI is usually the minimal optimal imaging modality. For patients who have tumours with 'pushing' margins extending into body cavities (e.g. abdomen, thorax), GTV will required modification, because with regression of the tumour, normal tissues such as bowel and lung will have returned to their normal position.

4.1.2. CTV

CTV should encompass any sites of potential microscopic extension of GTV, and should be at least GTV + 1.5 – 2cm (depending on exact anatomical location). It should also take into account anatomical barriers to tumour spread such as fascial boundaries and bone.

4.1.3. PTV

PTV is defined from CTV, with a margin to account for day-to-day set-up variation, and if relevant, internal organ motion. This will vary according to tumour location in the body, and is specific to individual institutions. PTV will be typically 0.5 – 1.0cm.

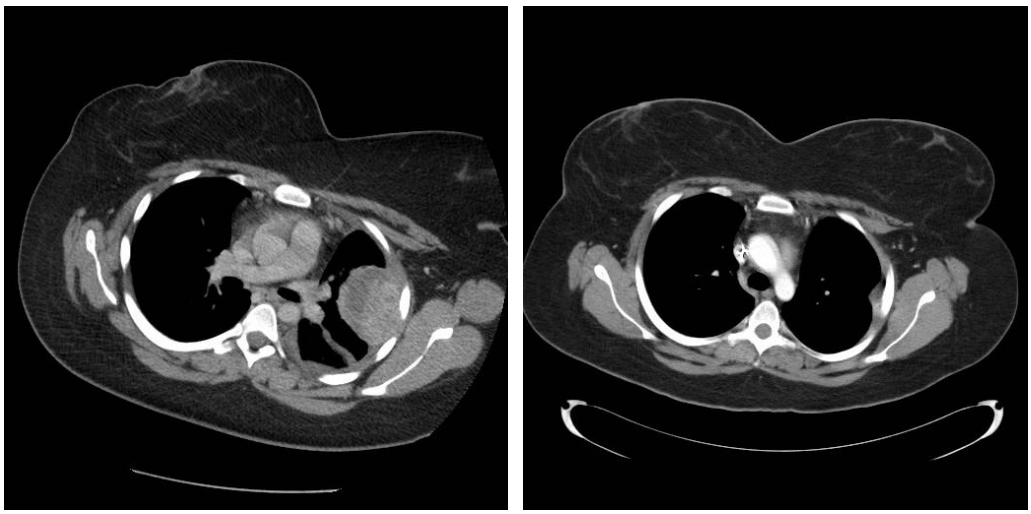
4.2. Post-operative radiotherapy

4.2.1. GTV

For patients who have undergone surgery, there is by definition no GTV, but consideration should be given to reconstructing the pre-treatment GTV to aid decisions made in the voluming of CTV.

GTV is defined as the visible tumour on imaging at its maximal extent (using CT, PET, bone and MRI scans, as available) prior to any chemotherapy or surgery. MRI is usually the minimal optimal imaging modality. For patients who have tumours with 'pushing' margins extending into body cavities (e.g. abdomen, thorax), GTV will required modification, because with regression of the tumour, normal tissues such as bowel and lung will have returned to their normal position.

Figure 1: Ewing's sarcoma of rib, demonstrating returning of lung to normal position following regression of tumour on induction chemotherapy.

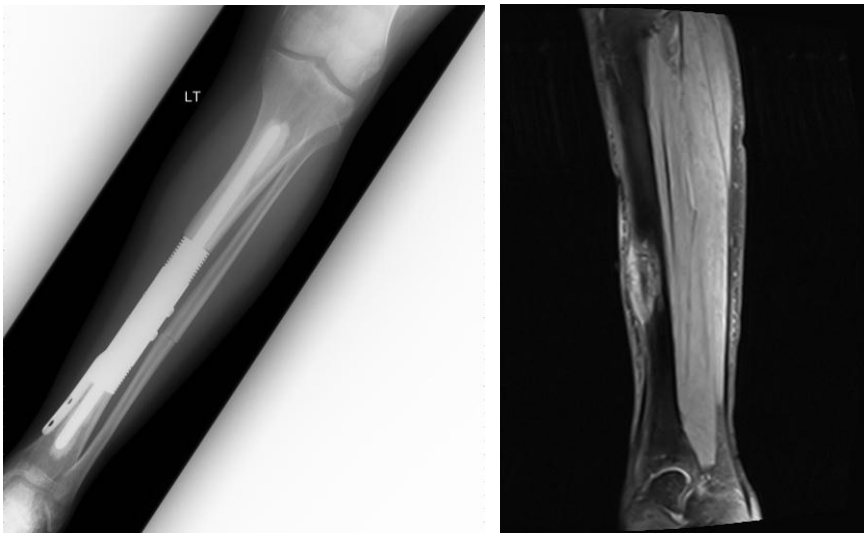


4.2.2. Clinical target volume 1 (CTV1)

CTV1 should encompass any sites of potential microscopic extension of GTV, or of contamination by GTV, including metallic prostheses, drain sites and surgical scars (if feasible), and should be at least GTV + 1.5 – 2cm radially (depending on exact anatomical location). It should also take into account anatomical barriers to tumour spread such as fascial boundaries and bone. It may not be necessary to treat the entire prosthesis, depending on its structure and size; this should be decided on an individual patient basis, balancing the need to include the prosthesis, and the

resulting additional normal tissue that must be treated to achieve this. Similarly, it may not be necessary or possible to treat the entire scar, particularly if its inclusion results in a significant increase in treatment volumes with a resultant anticipated increase in the morbidity of radiotherapy.

Figure 2: Ewing's sarcoma of tibial shaft, with large prosthesis that would not need to be completely included in CTV.



4.2.3. Clinical target volume 2 (CTV2)

As with CTV1, CTV2 should encompass any sites of potential microscopic extension of tumour (GTV), and should be no less that GTV + 1 – 2cm (depending on exact anatomical location). However, CTV2 does not need to include scars and drain sites. It should take into account anatomical barriers to tumour spread such as fascial boundaries and bone.

4.2.4. Planning target volume 1 and 2 (PTV1/2)

PTV1 and 2 are defined from CTV 1 and 2 respectively, with a margin to account for day-to-day set-up variation, and if relevant, internal organ motion. This will vary according to tumour location in the body, and is specific to individual institutions. PTV1 and 2 will be typically 0.5 – 1.0cm.

4.3. Whole lung radiotherapy

The CTV is the entire pleural cavity/surface of both lungs. A margin, usually at least 1cm is added for PTV. Volumes can be drawn, or alternatively treatment fields can be placed by simulation or virtual simulation. Respiratory-gated radiotherapy can be used if desired.

5. Radiotherapy dose and fractionation

5.1. Pre-operative radiotherapy

The total dose for preoperative irradiation is 50.4 Gy in 28 fractions in a single phase to the PTV. If there are concerns about organ tolerance or wound healing, then this dose can be reduced to 45 Gy in 25 Gy fractions.

5.2. Post-operative radiotherapy

The total dose for postoperative radiotherapy is 54 Gy in 30 fractions, delivered as 45 Gy in 25 fractions to PTV1, and 9 Gy in 5 fractions to PTV2.

5.3. Definitive radiotherapy

The total dose for definitive radiotherapy is 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. A boost of 5.4Gy in 3 fractions may be considered if desired, keeping within standard normal tissue dose constraints.

5.4. Whole lung radiotherapy

The dose for whole lung radiotherapy is 15 Gy in 10 fractions for patients <14 years, or 18 Gy in 12 fractions for patients ≥14 years. Dose may be specified to 100% for an optimised plan, or to the mid plane dose (MPD) for simulated opposed fields. However, it should be noted that this will result in a dose of approximately 10% higher in the lungs than that prescribed, and so optimisation of dosimetry is recommended if fields are simulated.

5.5. Fractionation

Conventionally fractionated radiotherapy (once daily fractions, five 1.8 Gy fractions per week) is the preferred fractionation schedule. In very young children, fractionation using 1.6Gy fractions may be considered.

6. Considerations for specific tumour locations

6.1. Extremity tumours

The limb should be immobilised with a customised immobilisation device. Care should be taken to include any adjacent skip metastases. The CTV along the length of the bone should be 1 – 2 cm beyond GTV in the bone, and 2 cm beyond the pre-chemotherapy extra-osseous mass. Joints and epiphyseal plates should be spared if possible, as long as this does not compromise PTV coverage. An un-irradiated strip of normal tissue ('corridor') along the length of the limb should be spared in order to maintain lymphatic drainage and to reduce the risk of lymphoedema. There are no data to allow definition of the width or volume to be spared as the corridor, but it is suggested that it should be approximately 0.25 of the circumference, which equates to approximately 10% of the cross-sectional area of the limb. For IMRT, VMAT or tomotherapy plans, attention should be paid to limiting the dose to areas outside PTV1, and to limiting a corridor as described above to no more than 35 Gy.

6.2. Tumours of the head and neck and skull

Patients with head and neck/skull tumours should be immobilised with a customised immobilisation device. The margins added to GTV for CTV may be smaller than 1.5 – 2cm, as such margins are unlikely to be achievable because of local critical structures (e.g. eye, optic chiasm). CTV to PTV margins are also expected to be smaller due to the better immobilisation possible at these locations. Head and neck/skull tumours are likely to benefit from an IMRT/VMAT plan.

6.3. Pelvic/sacral tumours

Pelvic and sacral tumours will frequently present with large pre-chemotherapy tumour volumes that extend into the pelvic and abdominal cavities. These tumours can regress significantly, with normal tissues such as bowel returning to their normal locations. Voluming of GTV and CTV will need to take this into account so that large volumes of normal tissues are not treated un-necessarily. Surgical placement of spacer devices may be helpful, in order to displace bowel away from the involved bone. Pelvic and sacral tumours may benefit from an IMRT/VMAT plan.

6.4. Chest wall/rib tumours

These tumours may also present with large pre-chemotherapy tumour volumes that extend into the thoracic cavity, displacing lung and pleura. Regression of the tumour during induction chemotherapy often result in lung returning to its normal location, and voluming of GTV and CTV will need to take this into account to avoid unnecessary treatment of large volumes of lung. If pleural involvement was observed at presentation with a pleural effusion (even if cytology was negative), then the whole pleural cavity of the hemithorax will need to be included, treated as for the guidelines for whole lung radiotherapy. Hemithorax radiotherapy is then followed by treatment of GTV to a total dose of 54 Gy if radiotherapy to the primary site is indicated.

6.5. Spinal/paraspinal tumours

GTV should be treated with an appropriate margin around any soft tissue extension, and should receive a maximum dose of no more than 50.4 Gy in 28 fractions. CTV should normally include one unaffected vertebra above and below the affected vertebra, and should also include the scar and any metallic stabilisation rods and cages if the patient has had surgery (as long inclusion of these does not increase the CTV to an unreasonably large size); a smaller CTV2 can be used if appropriate, that does not completely encompass scars, and rods and cages. PTV1 should be treated to a dose of 45 Gy in 25 fractions, and PTV2 to a dose of 5.4 Gy in 3 fractions. Otherwise, PTV is treated in a single phase to a total dose of 50.4 Gy in 28 fractions.

Spinal and paraspinal tumours may benefit from an IMRT/VMAT/tomotherapy plan, in order to achieve optimal doses to PTV while keeping the spinal cord dose within tolerance. However, the presence of metal rods and cages may produce dosimetric uncertainties when using IMRT/VMAT/tomotherapy techniques, which should therefore be used with caution.

7. Chemotherapy during radiotherapy

7.1. Actinomycin D

Actinomycin D given during VAC and VAI consolidation chemotherapy (arm A) should be omitted during central axial irradiation, or where there are concerns for acute toxicity that may be exacerbated by actinomycin D. It can be re-introduced again on completion of radiotherapy. Radiotherapy should start no sooner than 1 week after the last dose of actinomycin, and actinomycin should be re-introduced no sooner than 1 week after completion of radiotherapy.

7.2. Doxorubicin

Doxorubicin given during VDC chemotherapy (arm B) should be omitted during radiotherapy, and can be reintroduced on completion of radiotherapy. Radiotherapy should start no sooner than 1 week after the last dose of doxorubicin, and doxorubicin should be re-introduced no sooner than 1 week after completion of radiotherapy. Longer delays (up to 3 weeks) should be used if bowel or heart are within the radiotherapy fields.

8. Dose limits to normal tissues

Clinicians are referred to the recent QANTEC publication for limits to normal tissues (1).

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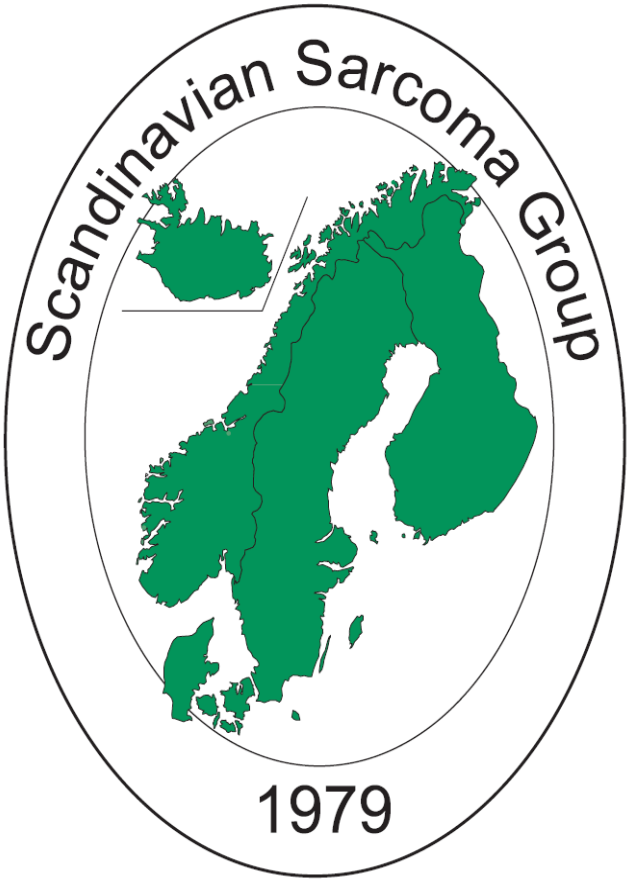
Scandinavian Sarcoma Group

SSG XXIV
Recommendations for Radiotherapy in Bone- and Soft Tissue Sarcoma



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1 Introduction

Radiotherapy (RT) is frequently indicated as part of curative treatment of bone and soft tissue sarcoma to improve local control, or, in palliative settings to relieve symptoms. Hence, RT may be administered pre- (neo-adjuvant) or postoperatively (adjuvant); as the sole and definitive local treatment in radiosensitive sarcoma types; in cases of inoperable primary tumours; or, in circumstance of metastases causing local symptoms.

Typically, fractionated RT using photons and/or electrons are applied. In some circumstances, in particular in children in case of a sarcoma in close relation to structures of the central nerve system, particle therapy may yield superior conformity and organs-at-risk avoidance. Brachytherapy is another technique facilitating normal tissue sparing in selected cases. Given the diversity of anatomical localisation and histological tumour subtypes representing the heterogeneous biological features of sarcomas, individualised conformal 3D-RT is customary. Current inverse treatment planning techniques based on advanced imaging methods are useful to balance the effects and potential side-effects of RT, although the scientific evidence for comparisons of the different techniques is limited.

The Scandinavian Sarcoma Group (SSG) recommendation for the use of RT in treatment of the different sarcoma subtypes are based on available clinical evidence, Scandinavian experience, and international and Scandinavian practice guidelines. This document comprises radiation treatment specifications applicable for clinical scenarios in general, and guidelines for RT in soft tissue sarcoma in adults in particular. Additionally, we refer to recommendations according to the specific on-going bone sarcoma and paediatric sarcoma treatment protocols in which SSG participate. We encourage inclusion of sarcoma patients in clinical studies whenever possible. The most relevant studies/treatment guidelines are summarized in Table 1.

Sarcoma subtype	**Protocol**
High-risk soft tissue sarcoma (STS), adults	SSG XX
Soft tissue sarcoma < 21 years	EpSSG RMS 2005, EpSSG NRSTS 2005, EpSSG RMS MET 2008, CWS-guidance 2014
Osteosarcoma < 40 years	Euramos 1
Osteosarcoma > 40 years	Euroboss 1
Ewing's sarcoma, ≤ 40 years: Non metastatic High-risk	 ISG/SSG III ISG/SSG IV
Ewing's sarcoma ≤ 50 years	Ewing 2008

Table 1. Adjuvant treatment protocols or recommendations currently used in SSG

1.1 *General considerations*

The following specifications of treatment prescriptions are applicable for all tumour categories, but should be customised for each individual patient. The background, indications and recommendations for RT are outlined in separate chapters based on anatomical locations and sarcoma histotypes. Those sections have been concluded with a brief summary of the main therapeutic implications.

1.2 *Specification of treatment prescriptions*

1.2.1 *Introduction*

The layout of these treatment prescriptions are largely based on the 2014 report from the Swedish Radiation Safety Society including a template for external beam radiotherapy protocols, and adapted for the purpose of guidelines for treatment of soft tissue and bone sarcomas.

When patients are included in specific treatment protocols, the respective protocol guidelines for RT should be consulted. Collaboration with the operating surgeon is fundamental when planning and executing RT in soft tissue and bona sarcoma patients.

1.2.2 *Patient fixation*

To reduce the set-up errors during treatment, care should be taken to ensure adequate fixation of the patient and affected body region to be treated. The position must be reproducible during planning, simulation and treatment. Because optimal fixation is difficult to standardize (prone, supine, thorax-fix, joint extension or flexion etc.), a close collaboration between oncologists, radiation therapists and physicists with experience in sarcoma treatment is essential.

In the pre-treatment preparation (simulation), immobilisation devices should be used for reproducible positioning. The patient reference coordinate system is defined by using tattoos during preparatory imaging.

1.2.3 *Patient data acquisition or pre-treatment imaging*

For structure delineation, a CT study should be performed in the treatment position on a flat table top with the patient, or the affected body region to be treated, in the fixation device. If available and needed, MRI or PET/CT in the same position can be used, as well as time resolved 4D imaging technique or respiratory gating if applicable. The scan should be confined by anatomical landmarks and registration technique should be specified. The need and use for intravenous or oral contrast medium, or the use of tracer, must be evaluated form the diagnostic images and predefined. In postoperative setting, the scar should be marked with a lead thread. The CT scanning for treatment planning calculations should include the complete circumference of the involved body part (and if necessary both legs, although efforts should be made to exclude the healthy extremity from the RT fields), and performed as a volume according to the protocols of the local radiology department. Reformations with a slice thickness of maximum 5 mm, preferably 3 mm, are made from the volume. The examination should be stored in the PACS. External or internal reference systems for image guided RT

(IGRT) should be well defined. Reference imaging with planar kilovoltage (kV) or megavoltage (mV) images, or cone beam CT (CBCT) datasets, are matched with the planning CT datasets or digitally reconstructed radiographs (DRRs).

1.2.4 *Target volumes and organs-at-risk (OAR) volume specification*

In study patients, the target volumes should be delineated in accordance with the respective protocol definitions. Otherwise, the definition of volumes should follow the recommendations made by the International Commission on Radiation Units and Measurements, ICRU, for photon and electron beam therapy (ICRU reports 50, 62, 71 and 83).
We recommend that the naming of target and OAR volumes follow the standardized Swedish nomenclature for RT (Swedish radiation Safety Authority; Report 2014:25), which is based on ICRU 83 and Santanam et al. (2012), Table 2 (see: www. Stralsakerhetsmyndigheten.se), [1].

Naming of Target Volumes		
Name	Type	Comment
GTVT_xx.x (free text)	Single/primary	xx.x = dose in Gy
GTVT1_R_xx.x (free text)	Multiple/primary	T1, T2 etc. L=left, R=right
GTVT2_L_xx.x (free text)		
GTVN_xx.x (free text)	Single/node	
GTVN1_R_xx.x (free text)	Multiple/node	N1, N2 etc, L=left, R=right
GTVN2_L_xx.x (free text)		
CTVT_xx.x (free text)	Etc.. (similar to GTV)	
ITVT_xx.x (free text)	Etc.. (similar to GTV)	
PTVT_xx.x (free text)	Etc.. (similar to GTV)	

Table 2. Naming of target volumes according to Swedish radiation Safety Authority; Report 2014:25, based on ICRU 83 and Santanam 2012 [1].

GROSS TUMOR VOLUME (GTV)

In preoperative RT, the macroscopic tumour volume is visualized on the CT-images for treatment planning, co-registered with MRI and/or PET/CT examinations preferably performed in the treatment position. The GTV may be defined as a sum (boolean technique) of delineated GTVs from different imaging modalities (CT, MR, PET) [2].
If multiple primary tumour nodules or positive lymph nodes are present, separate GTV volumes are defined, and labelled GTV-T1, GTV-T2, etc. and GTV-N1, GTV-N2, etc., respectively (see Table 2 or ICRU 71).

In postoperative RT, the surgical bed may be difficult to define. Co-registration of the planning CT with preoperative radiologic images enables reconstruction of a the resected GTV representing the initial tumour boundaries and the proximity to, or involvement of, adjacent anatomical structures. This should preferably be carried out together with the radiologist as the anatomy of the compartments has changed. Note that OARs may be closer to the target volumes postoperatively. A close collaboration between the oncologist and the sarcoma surgeon is compulsory.

CLINICAL TARGET VOLUME (CTV)

The CTV is defined by means of the preoperative tumour bed as defined on diagnostic MR and

findings at surgery. Recommendations for the safety margins will most often be defined in the respective protocols. Regarding STS in adults, a transverse margin of 1.5 cm and 4 cm longitudinally to the GTV is proposed, according to Haas et al (see section 2.1.3) [3].

Postoperative MRI-sequences demonstrating oedema (STIR) may be helpful in segmenting the CTV. On should make an effort to include peritumoural oedema seen in T2 MR sequence in both pre- or postoperative RT. Whether it is necessary to include in the CTV the complete and potentially contaminated compartment, drainage canal, overlying scar and postoperative oedema/hematoma/seroma should be discussed with the radiologist and the operating surgeon. Radio-opac surgical clips may be of help to define critical borders of the tumour bed. The quality of the surgical margin will be of relevance, as poorer surgical margins motivate more liberal volumes compared with wide margin surgery.

Intact fascial linings (muscle fascia, periosteum, nerve sheaths etc.) serve as barriers for tumour spread, and may be pertinent to restrict the CTV in certain directions, or to delineate whole compartments that should be encompassed by the CTV if tentatively contaminated. If underlying fascial borders or periosteum are uninvolved, they may serve as CTV constraints with no further CTV-extensions in this direction. Otherwise, a 10 mm margin is considered adequate. If multiple primary tumour nodules or positive lymph nodes are present, separate CTV volumes are defined and labelled CTV-T1, CTV-T2, etc. and CTV-N1, CTV-N2, etc., respectively (see Table 2 or ICRU 71).

The scar should be included in the CTV with an additional margin (of typically 2 cm) at both sides (with the use of bolus if necessary, see section 1.2.8), if the tumour has been removed with intralesional surgery (including spilling). A lead wire should be taped along the entire length of the scar during CT simulation. Furthermore, the scar overlying the GTV should be included in the CTV in case of tumour infiltration in the skin or subcutaneous tissue, unless the affected skin has been removed by a sarcoma surgeon en-bloc together with the tumour. The scar may be excluded from the CTV following negative margin surgery of deep-seated tumours.

INTERNAL TARGET VOLUME (ITV)

In order to compensate for uncertainties regarding size, shape and in particular the position of the CTV in the internal anatomical landscape, an optional ITV-margin may be added to compensate for organ-movement such as respiration.

PLANNING TARGET VOLUME (PTV)

PTV is typically defined as the CTV with an additional isotropic margin of 1 cm, although specific protocols may recommend otherwise. The PTV may be customized according to anatomical location, immobilisation, reproducibility and 2D or 3D on board imaging technique. A smaller PTV margin than 10 mm is often justifiable with satisfactory immobilisation and intimacy of the CTV with critical structures.

ORGANS-AT-RISK (OAR)

Delineation of all relevant organs at risk is recommended as a basis for treatment plan optimisation, and for documentation and reporting of dose-volume parameters. For extremity localization, avoid circumferential irradiation to reduce the risk for subsequent distal lymphedema. Using IMRT, a low dose to the whole circumference may be acceptable (a dose of 20 Gy is probably safe). Avoid inclusion of an entire joint space and full-dose irradiation of adjacent bone of the weight bearing skeleton to reduce the risk of pathologic fractures. A dose constraint to weight bearing bones of V40 < 65%, mean dose 37 Gy, max dose 59 Gy) has been suggested [4].

PLANNING ORGAN-AT-RISK (PRV)

A planning organ-at-risk volume (PRV) should be defined for OARs with a serial architecture (e.g. optic chiasm, spinal cord, etc.) by adding a proper margin to the OAR.

TARGET MOTION

Target and organs-at-risk motion should be taken into account by using sufficient ITV margins, and/or facilitated by 4D-CT, gating, etc.

The risk of late radiation morbidity must be taken into account for the various critical OARs. Estimated dose levels concerning toxicity of normal tissues and organs are available from e.g. the QUANTEC report (see Table 4) [5-7].

1.2.5 *Radiation treatment technique*

It is left to each centre to decide on the type of treatment delivery technique (3DCRT, IMRT, VMAT, tomotherapy, brachytherapy, protons) as long as the dose-volume constraints are fulfilled [8].

1.2.6 *Dose specification and dose-volume constraints*

Dose specification should be based on a prescription priority list according to relevant protocol (e.g. Table 3) and/or updated reports such as the QUANTEC (Table 4) [7] which also serves as a tool for treatment plan optimisation, by prioritising objectives and constraints for the various volumes of interest. Dose reporting should be in accordance with ICRU recommendations (see e.g. ICRU 83). For electron treatment the dose at the depth of dose-maximum (D_{max}) at a perpendicular angle to the surface should be used for dose specification and dose reporting (see ICRU 71). The energy should be chosen so that the PTV is encompassed by the 90% isodose level.

Dose to critical organs

The dose to kidney, heart, liver, lung, and spinal cord shall be calculated. Doses to the critical organs should not exceed the maximum values listed below:

spinal cord	45 Gy
heart	30 Gy to more than 50% of its volume
liver	30 Gy to more than 50% of its volume
lung	20 Gy to the whole lung
kidney	14 Gy to the whole kidney

Table 3. Example of dose-volume constraints priority list (from ISG/SSG III)

QUANTEC summary data for organ-specific dose/volume/outcome data						
Organ	Volume	RT type	Endpoint	Dose (Gy) or Dose/Volume	Rate (%)	Notes
Spinal cord	partial	3D-CRT	Myelopathy	Dmax = 50	0.2	Full cross section
	partial	3D-CRT	Myelopathy	Dmax = 60	6	
	partial	3D-CRT	Myelopathy	Dmax = 69	50	
	partial	SRS	Myelopathy	Dmax = 13	1	Partial cross section
Heart	Pericardium	3D-CRT	Pericarditis	Mean = 26	< 15	
	Pericardium	3D-CRT	Pericarditis	V30 < 46%	< 15	
	Whole	3D-CRT	Cardiac mortality	V25 < 10%	< 1	
Liver	Whole	3D-CRT	RILD	Mean < 42	< 50	
	Whole	3D-CRT	RILD	Mean < 28	< 5	
	Whole	SBRT	RILD	Mean < 15-20	< 5	
	> 700 cc	SBRT	RILD	Dmax < 15	< 5	
Lung	Whole	3D-CRT	Pneumonitis	V20 ≤ 30	< 20	Combined lung
	Whole	3D-CRT	Pneumonitis	Mean 7	5	
	Whole	3D-CRT	Pneumonitis	Mean 13	10	
	Whole	3D-CRT	Pneumonitis	Mean 20	20	
	Whole	3D-CRT	Pneumonitis	Mean 24	30	
	Whole	3D-CRT	Pneumonitis	Mean 27	40	
Kidney	Bilat whole	3D-CRT	Dysfunction	Mean 15-18	< 5	
	Bilat whole	3D-CRT	Dysfunction	Mean < 28	< 50	
	Bilat whole	3D-CRT	Dysfunction	V12 < 55%	< 5	Combined kidney
				V20 < 32%	< 5	
				V23 < 30%	< 5	
				V28 < 20%	< 5	

Table 4. Example of corresponding QUANTEC data (ref. Table 3), data form: Marks et al., IJROBP (2010) [7]. Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy, SRS= single fraction, RILD = radiation induced liver damage, SBRT = stereotactic RT

1.2.7 *Fractionation and treatment time*

RT is typically given as daily fractions. Accelerated RT according to for instance SSG XX or ISG/SSG III and IV is administered twice daily with at least 6 hours interval between two daily fractions. Boost is typically given in a sequential schedule. Simultaneous integrated boost (SIB) may be an alternative in VMAT or IMRT. Unintended interruptions should be compensated within the intended overall treatment time according to the BED/EQD2 concept.

1.2.8 *Use of bolus material*

Bolus is recommended in cases of intralesional margin and following marginal resection of tumours with diffuse infiltration of the skin or subcutaneous tissue (unless the skin is excised en-bloc with the tumour) to ensure therapeutic dose to the scar with a 2 cm margin on both sides, i.e. a 2 cm perimeter of the skin on both sides of the scar is included in the CTV/PTV. Bolus may be considered following a primary resection or incisional biopsy performed outside a sarcoma centre. It may be practical to mount the bolus material during the CT simulation procedure, in particular when the fixation equipment will be in direct contact with the scar area.

1.2.9 *Relation to other concomitant therapies*

The timing (pre-, postoperatively) relative to surgery or drug therapy, as well as the exact interval between commencement of the combined modalities, should follow current treatment protocols. In case of adjuvant RT outside of clinical studies, these factors should be discussed individually. Generally, the time lapse between surgery and RT should be in the range of 3-6 weeks. In preoperative RT, the patients must have recovered from acute reactions at the time of surgery. In postoperative RT, the wound healing must be satisfactory prior to commencement of adjuvant RT. Factors motivating preoperative RT are large, locally advanced tumours in close proximity to critical structures (which typically is the case in upper extremity sarcomas, retroperitoneal sarcomas and head-and neck location (see also section 2.1.1). Doxorubicin increases the RT toxicity; concomitant use should be avoided, and careful assessment of acute toxicity performed when doxorubicin is given sequential to RT (e.g. SSG XX). A minimal interval between doxorubicin and radiotherapy should be 7 days. Likewise, Actinomycin-D should be avoided during RT.

1.2.10 *Dose computation*

The size and resolution of the calculation grid should be ≤ 3 mm.

1.2.11 *Image-guided and adaptive treatment delivery*

Image-guided and adaptive treatment delivery, if applicable, should be performed according to institutional practice. Evaluation of tumour response should be based on radiological imaging after the completion of RT according to the specific treatment protocol.

1.2.12 *Quality management*

Quality assurance and quality controls throughout the RT process shall be performed according to institutional practice.

Dummy runs are advised before commissioning of new treatment protocols.

2 Soft tissue sarcoma (STS)

2.1 *General considerations*

The following section is applicable for the adult population. Specific guidelines for the treatment of children, adolescents and young adults are provided by the EpSSG NRSTS and EpSSG RMS (both 2005) and the EpSS RMS-MET (2008), as well as the CWS-guidance (2014) (see: Radiotherapy in paediatric sarcoma, chapter 4).

2.1.1 *Indications for radiotherapy*

Scandinavian guidelines for adjuvant RT in extremity and trunk wall soft tissue sarcoma (STS) in adults were initially outlined in the SSG XIII protocol of 1998 [9]. This protocol was however concluded in 2007, and the succeeding SSG XX only holds recommendations for high-risk scenarios. The present document serves as current recommendations for all risk categories, based on Scandinavian practice and scientific reports.

SSG XX was closed for inclusion in 2014. While awaiting the results, the SSG oncology group recommends that patients fulfilling the high-risk inclusion criteria are treated according to SSG XX with accelerated RT interposed with adjuvant chemotherapy (see section 2.2.1).

The surgical margin is an important parameter in the decision making of applying adjuvant RT, and the classification of surgical margins currently used in SSG is as follows, Figure 1 (see SSG VII: 4 and SSG XX):

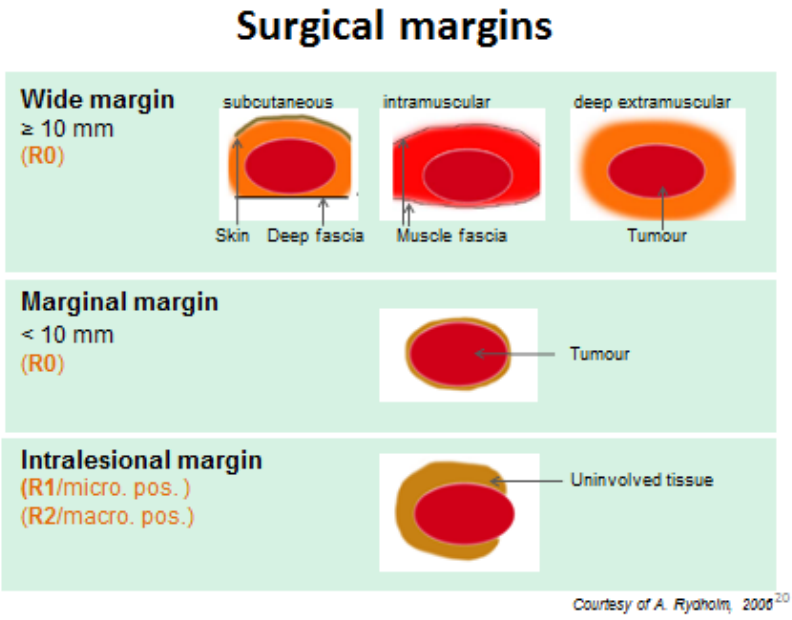

Figure 1, surgical margin classification, SSG VII:4.

Negative surgical margin:

1) wide, i.e. unengaged fascia or a cuff of 10 mm healthy tissue around the entire circumference of the tumour, or

2) marginal, i.e. less than a wide margin (only few mm) but microscopically uninvolved.

Positive surgical margin:

1) gross tumour left or tumour leakage reported by the surgeon, or

2) intralesional, i.e. microscopic tumour tissue at the resection border detected by the pathologist.

The effects of adjuvant RT is well documented in high-grade extremity and trunk wall soft tissue sarcoma (ETSTS) excised with non-wide margins [10-13]. Evidence has emerged showing that RT improves local control also in deep-seated high-grade malignant tumours removed with a wide margin [13, 14]. Findings based on data from the SSG-register have confirmed the effect of adjuvant RT, with improved local control following RT even in low-grade STS (Table 5) [15]. Local control in subcutaneous low-grade STS given postoperative RT following intralesional surgical margins was 93%, compared with 82% in patients who underwent surgery alone. In deep-seated low-grade STS, local control rates following intralesional surgery was 90% and 75% with and without adjuvant RT, respectively.

		Without RT *(n=622)*	**RT** *(n=453)*
Subcutaneous, low-grade	Wide margin	0.97	0.99
	Marginal margin	0.97	0.99
	Intralesional margin	**0.82**	**0.93**
Subcutaneous, high-grade	Wide margin	**0.86**	**0.95**
	Marginal margin	**0.67**	**0.87**
	Intralesional margin	**0.38**	**0.71**
Deep, low-grade	Wide margin	0.96	0.98
	Marginal margin	**0.89**	**0.96**
	Intralesional margin	**0.75**	**0.90**
Deep, high-grade	Wide margin	**0.80**	**0.93**
	Marginal margin	**0.57**	**0.82**
	Intralesional margin	**0.26**	**0.62**

Table 5. Five-year local control rates by prognostic group and radiotherapy in 1093 patients with extremity and trunk wall soft tissue sarcoma. Source: Jebsen et al, 2008.

There is consensus that adjuvant RT is indicated in all high-grade STS following marginal and intralesional margin surgery, and after wide margin surgery in deep-seated, high-grade tumours [16, 17]. Furthermore, RT is recommended by SSG in low-grade STS excised with an intralesional margin.

In addition, RT may be considered in cases of marginal margins in deep-seated, low-grade STS, or wide margins in subcutaneous STS if surgical resection of a local recurrence would be mutilating. RT is usually not recommended following wide margin surgery of low-grade STS, or after marginal surgery in subcutaneous, low-grade STS.

RT may be offered as definitive treatment in technically or medically inoperable cases, or if the patient declines surgical treatment [18, 19].

Preoperative RT seems equivalent to postoperative RT regarding local control and long-term physical function [20-22]. However, the risk of post-operative wound complications is higher in preoperative RT [22]. The size of the target volume is correlated with the risk of late radiation morbidity. Hence, preoperative RT may be advantageous when the risk of wound complications is considered low, and the target volume must be restricted to shield vulnerable structures (STS in upper extremity, retroperitoneal sarcoma, head- and neck location) [20, 23-25]. Furthermore, preoperative RT may be applied in large, infiltrative tumours in close proximity to nerves and vessels to facilitate function preserving surgery [16, 26].

Timing of adjuvant RT in adult extremity and trunk wall STS:

Postoperative RT is recommended regardless of surgical margin in high-grade, deep-seated STS, and following marginal and intralesional surgery in all high-grade STS irrespective of tumour depth (Table 6). Furthermore, RT is indicated after intralesional surgery irrespective of malignancy grade.

Preoperative RT may be considered in large, locally advanced tumours to support limb sparing, marginal surgery, or if target volumes are believed to be considerably smaller with neo-adjuvant treatment.

2.1.2 *Dose fractionation schedules*

There is no consensus on RT dose among various international guidelines [9, 15-17]. In Scandinavia, a total dose of 50 Gy has been routine following marginal or wide margin surgery, in contrast to typically 60 Gy outside Scandinavia. The fraction dose is normally 2 Gy, although 1.8 Gy is occasionally preferred, in particularly in the paediatric population. Despite the fact that Scandinavian practice represents lower doses compared with European and North-American recommendations, local control rates seems similar following negative margin surgery [15, 27-32]. Also in intralesional surgery, higher RT dose levels have been used outside SSG, resulting in seemingly better local control rates [27, 30]. Thus, there might be a potential in SSG to improve local control following intralesional surgery in STS by applying a larger boost dose of up to 16-20 Gy (in contrast to the customary boost dose of 10 Gy) to a restricted high-risk volume [12, 28, 33]. We recommend a postoperative dose of at least 66 Gy following intralesional margin surgery. An SSG-study of 1093 patients with ETSTS diagnosed 1986-2005, of whom approximately 40% underwent RT, revealed significant differences in local control rates between all three margin types (wide, marginal and intralesional) [15]. A later study including 462 patients (diagnosed 1998-2009), all given RT, did not demonstrate a significant difference in local control between wide and marginal margin – only between wide and intralesional margin [32]. A conceivable explanation is a higher rate of planned marginal margins in the later years motivated by the evidence that adjuvant RT may to some extent compensate for non-wide margin surgery. Based on this assumption, and in cases of for

instance unplanned marginal margin surgery, a higher dose than 50 Gy/25 fractions may sometimes be justified.

In cases of technically or medically unresectable STS, definitive RT to dose-levels exceeding 63 Gy in 2 Gy fractions may be advocated when feasible, as high dose levels in this setting is reported to increase the probability of local control [18, 28, 34]. Local tumour control is correlated with the total RT dose administered; however, since the rates of complication rise parallel with the increased RT dose, considerations of dose to organs at risk may be outweighed by the potential benefits of high dose levels. Intra-abdominal location of the sarcoma is particularly challenging because of the close proximity to vulnerable parenchymatous organs or intestine. Consequently, a dose beyond 50 Gy is often prohibited in definite RT of retroperitoneal or abdominal/pelvic sarcoma.
Depending on circumstances such as patient age and co-morbidity, a more palliative approach in case of an unresectable localised tumour will be hypo-fractionation, e.g. 3 Gy x 13-15.

Recommendation adjuvant RT in extremity or trunk wall STS (Table 6):

Negative surgical margin: 50 Gy, 1.8 to 2.0 Gy daily fractions

Positive surgical margin: 50 Gy to tumour bed with an additional boost of 10-20 Gy to total doses of 60-70 Gy (aiming at minimum 66 Gy), 1.8 to 2.0 Gy daily fractions

Recommendation definitive RT in extremity or trunk wall STS (Table 6):

64-70 (74) Gy,1.8 to 2.0 Gy daily fractions.

Grade FNCLCC G1-3	Margin	Depth	Radiotherapy
G1	Wide	sc/deep	No
G1	Marginal	sc	No
G1	Marginal	deep	Consider RT
G2-3	Wide	sc	Consider RT
G2-3	Wide	deep	RT 50 Gy/25 fractions
G2-3	Marginal	sc/deep	RT 50 Gy/25 fractions
G1-3	Intralesional: micro/macro positive	sc/deep	RT 60 -70 Gy (2 Gy fractions)
G1-G3	Inoperable	sc/deep	64-70 (74) Gy (2 Gy fractions)

Table 6. Recommendation for adjuvant radiotherapy in patients with extremity and trunk wall soft tissue sarcoma.

2.1.3 *Target volume definitions*

See section 1.2.4 for general recommendations for definitions of target volumes and organs at risk. There is limited clinical evidence available for establishing the optimal size of the safety margins; however, in 2012 an panel of radiation oncologists involved in sarcoma treatment led by R. Haas published a consensus review comprising numerical recommendations for the CTV and PTV margins in pre- and postoperative RT in extremity STS [3].

According to Haas and co-workers the CTV should be defined by means of the preoperative tumour bed as defined on diagnostic MR and findings at surgery with an additional transverse margin of 1.5 cm and 4 cm longitudinally to the GTV. However, substantial adjustments of the CTV taking into account the surgical scar, peritumoural oedema, postoperative seroma, fascial barriers, organ movement, fixation etc. are rather the rule than the exception (see section 1.2.4). For the use of bolus, see section 1.2.4.

The PTV is produced by expanding the CTV using an additional isotropic margin of approximately 1 cm.

2.2 *Distinctive clinical situations*

2.2.1 *High-risk STS of extremities or trunk wall:*

SSG have pursued a strategy of selecting high-risk ETSTS patients to undergo systemic adjuvant treatment [9, 35, 36]. In patients with high-risk STS of the extremities and trunk wall eligible for the adjuvant SSG XX protocol, accelerated RT interpolated with chemotherapy is scheduled, either postoperatively (group A), or in the neo-adjuvant setting if primary, complete resection of the tumour is not feasible (group B) (www.ssg-org.net).

High-risk STS is defined by high-grade malignancy, the presence of vascular invasion in the specimen, and/or at least two of the following: size ≥ 8 cm, necrosis or infiltrative growth pattern.

RT Group A (post-operative):
1.8 Gy twice daily to 36 or 45 Gy, depending on the surgical margin

Patients with wide margins for deep-seated tumours and marginal margins for all tumours will receive 36 Gy between chemotherapy cycle 3 and 4 (arm 2, Figure 1). Patients with intralesional margins will receive 45 Gy regardless of tumour depth (arm 3, Figure 1).
The fractionation schedule is 2 x 1.8 Gy/day, with minimum 6-hour interval between the two daily fractions, and if possible 5 treatment days per week. Due to the radiosensitizing effect of doxorubicin a minimal interval between doxorubicin and radiotherapy should be 7 days.
In the event of complications following surgery which necessitates postponing RT until all six chemotherapy cycles are completed, a standard fractionated regimen is recommended, see Table 6. The interval between surgery and RT may exceed 7 weeks without any significant increase in the risk of LR [15].

Figure 2a. Treatment schedule group A by arm 1, 2 and 3

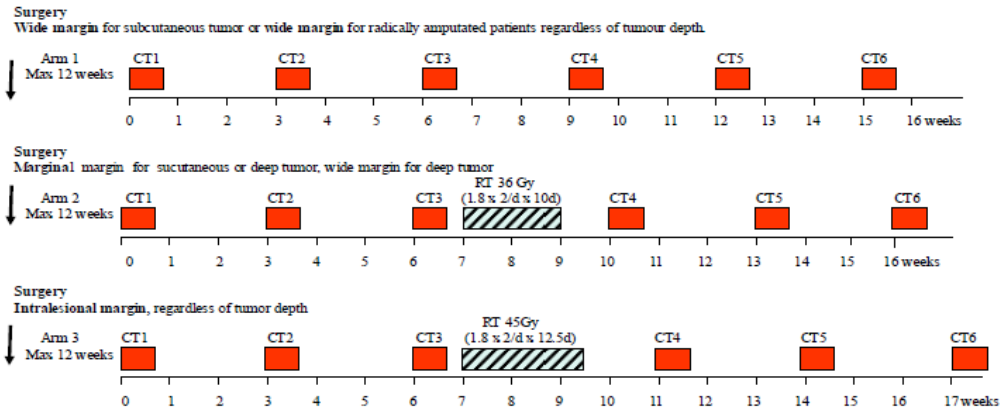

Figure 2.
Treatment schedule group A, SSG XX treatment protocol in high-risk soft tissue sarcoma of extremities and trunk wall.

RT Group B (pre- and postoperative):

1.8 Gy twice daily to 36 Gy

In case of an obvious risk of intralesional margin surgery, 3 cycles of chemotherapy as well as accelerated RT may be administered in the preoperative setting.
Radiotherapy (36 Gy) is given after the two initial chemotherapy cycles (Figure 2). The fractionation schedule is 2 x 1.8 Gy/day, with at least 6 hours interval between the two daily fractions, and if possible 5 treatment days per week. Due to the radiosensitizing effect of doxorubicin a minimal interval between doxorubicin and radiotherapy should be 7 days. Surgery is performed between chemotherapy cycle 3 and 4.

Figure 2b. Treatment schedule group B

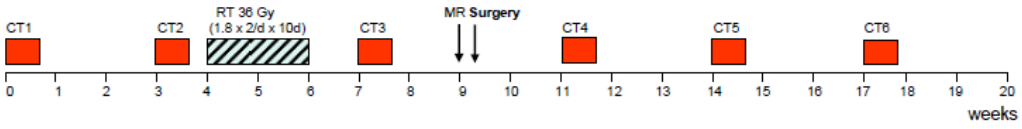

Figure 3.
Treatment schedule group B, SSG XX treatment protocol in high-risk soft tissue sarcoma of extremities and trunk wall.

Radiobiological considerations, SSG XX:

Accelerated tumour cell proliferation during prolonged radiotherapy regimes or treatment breaks may result in a risk of decreased local tumour control; hence RT treatment time should be as short as possible, without compromising wound healing, and within tissue tolerance for severe acute and late effects of radiotherapy.

In order to shorten the overall treatment period, the fractionation schedule in the SSG XX phase-II study is 2 x 1.8 Gy/day, with an interval between the two daily fractions of at least 6 hours in order to allow for repair of sub-lethal damage in normal tissue. The rather slow component of repair reported for some late responding tissues [37, 38], and thus the possibility of remaining incomplete repair, is taken into account by incorporating a dose per fraction modifying factor of 1.10 (ref SSG XIII) when establishing the total dose in the accelerated regimen used in the current protocol [38]. No such correction is deemed necessary for acute effects based on data for skin [38, 39].
When RT is given in combination with chemotherapy - doxorubicin and ifosfamide being radiosensitizers; both increased acute and late effects are to be expected. Concerning chemotherapy, a modifying factor of 1.15 was assumed for both early and late effects [40]. For estimates of early and late effects of RT, comparisons of Biologically Effective Dose (BED) were made for the conventional fractionation and the accelerated hyper-fractionated regime, see Protocol SSG XX, ssg-org.net. If the difference in overall treatment time is neglected, the schedules of accelerated RT to 36 or 45 Gy are equivalent to total doses regarding tumour effect of about 40 Gy and 50 Gy, respectively, or concerning late effects, 50 Gy and 60 Gy, if administered with conventional fractionation, i.e. one fraction of 2 Gy per day.

2.2.2 *Histotype-specific considerations*

Some reports suggest that for instance malignant peripheral nerve sheath tumour (MPNST) and epithelioid histopathological subtypes have a higher risk of LR, despite adjuvant RT [28, 32, 41]. Although this has never been confirmed in a randomized study (and probably never will be as such a study is hampered by the rarity of STS), it implies that a higher adjuvant RT dose may be considered in such seemingly radio-resistant histotypes if surgical resection of a local recurrence would entail mutilation/amputation.

Irradiation of lymph nodes in STS is not customarily undertaken as node involvement is rare. However, in subtypes such as epithelioid sarcoma, clear cell sarcoma or synovial sarcoma, elective irradiation of loco-regional lymph nodes may be considered if enlarged nodes/suspected involvement based on radiologic examinations are present, or metastases to lymph nodes are histologically confirmed.

2.2.3 *Difficult sites*

- *Retroperitoneum (see also section 5):*

Adjuvant RT in retroperitoneal sarcoma (RPS) is not routinely recommended due to the lack of clinical evidence of the efficacy of RT in this localisation. No randomized studies exist, and results from retrospective studies are conflicting [42-45]. Retrospective data from two Scandinavian centres, however, demonstrate an association between improved 5-year local recurrence-free survival and overall survival when surgical excision is combined with RT compared with surgery alone [46].

The optimal timing of administering RT in RPS is also controversial, i.e. whether preoperative, intra-operative or postoperative administration is the more appropriate approach. The theoretical rationale for preoperative RT is attractive as RT is administered while the primary tumour is displacing the adjacent healthy tissue beyond the radiation field. This may limit the radiation dose to abdominal viscera, which generally have low radiation tolerance. Preoperative RT in RPS is reported to be feasible and well-tolerated, and may be advocated in cases where a positive margin resection has been anticipated [47].

There is no consensus on target volume definitions in RPS treatment. The close proximity to intra-abdominal structures, and potentially very large target volumes, may preclude PTV margins applied in extremity tumours. Concurrently, organ movement due to respiration may call for additional ITV margins. In very large retroperitoneal STS planned for en-bloc-resection in which the retroperitoneal tumour origin represents a surgical challenge, with the tumour growth dislocating the intra-abdominal organs in a well demarked fashion, preoperative RT to 50 Gy to the retroperitoneal tumour origin, but not including the entire tumour circumference, may be considered to reduce the dose to OAR and facilitate surgery.

An adjuvant dose of 50 Gy (1.8 to 2.0 Gy fractions) is most often applied. Fraction doses of 1.8 Gy are encouraged when relative large volumes of intestine are encompassed by the PTV.

The European Organisation of Research and Treatment of Cancer (EORTC) is conducting a randomised clinical trial investigating preoperative RT (1.8 Gy x 28) versus surgery alone for resectable RPS. Participating centres in SSG are: Oslo University Hospital and Karolinska Hospital in Stockholm. We encourage participation in this study whenever the patients are eligible.

The recommendations for treatment of intra-abdominal, retroperitoneal and pelvine sarcoma SSG VII (2008) suggest adjuvant RT following intralesional surgery of RPS, provided that contamination of the peritoneal cavity has been avoided. RT to a total dose of 50 Gy (1.8 – 2 Gy per fraction) is most often used, which may be reinforced by a boost dose of 10 Gy to areas of positive margin.

In unresectable RPS, standard fractionated RT may be used as definitive treatment, yet signifying a palliative intent (serving to prolong time to progression) as the total dose will often be restricted by the tolerance dose to adjacent intra-abdominal organs. A dose-response relationship has been demonstrated in STS series including RPS, indicating that a dose > 63 Gy is correlated with superior tumour control [18]. High dose levels, however, implies an increased risk of complications, and the retroperitoneal location frequently precludes adequate doses and subsequently a definitive treatment approach. A total dose of 60 Gy or more should be attempted when feasible if local tumour control is the objective.

In palliative treatment for symptomatic lesions in advanced disease, hypofractionated regimens (3 Gy x 10-12 or 4 Gy x 5) are preferred to condense overall treatment time when life expectancy is highly limited.

Recommendation retroperitoneal sarcoma (RPS):

The Scandinavian Sarcoma Group (SSG) recommends participation in the currently running EORTC randomised clinical trial investigating preoperative RT versus surgery alone for resectable RPS.

In non-eligible cases, RT may be administered in patients with tumours of malignancy grades 3-4 and macroscopic or microscopic positive surgical margin, or anticipated intralesional surgery.

An adjuvant dose of 50 Gy in 1.8 – 2.0 Gy fractions is typically applied, which may be reinforced with a boost of up to 10 Gy in volumes of macroscopic positive surgical margins (see section 5).

In unresectable RPS, “definitive” standard fractionated RT to 60 Gy or more may be considered when feasible.

Palliative fractionation in symptomatic lesions: 3 Gy x 10-12 (or 4 Gy x 5)

- *Sarcoma of the breast:*

STS localized in the breast should be treated according to the same guidelines as STS in extremities or trunk wall. Total mastectomy including fasciectomy may be necessary to obtain adequate surgical margins. Dissection of the axillary lymph nodes is not routinely performed.

Phyllodes tumour of the breast represents a sarcomatous lesion containing both epithelial and connective tissue elements, however with a higher cell density of the stromal component. They may be classified as benign, borderline or malignant, of which the benign variant may be difficult to distinguish from a fibroadenoma. Recommended treatment is complete surgical resection with microscopic wide margins (10 mm or fascial lining). The local recurrence risk is correlated to the tumour size, excision margins and malignancy grade [48, 49]. In a series from Oslo University Hospital of 84 patients with Phyllodes tumour of the breast, including 55 of malignant type, no local recurrences were recorded following complete surgery with negative margins (R0) (Norwegian surgeon association, "Vitenskapelige forhandlinger, 2013"). In general, a re-excision should be performed if the primary resection results in positive margins. Radiotherapy reduces the risk of local recurrence, and is primarily indicated following contaminated margins in malignant tumours, although some centres follow the principles of treatment for other soft tissue sarcoma of the trunk wall, applying RT also following marginal surgery [50-52]. Based on the Oslo experience, adjuvant RT should be reserved for the rare patients in whom a re-excision after intralesional surgery cannot be performed for anatomical reasons (thoracic wall) or to whom mastectomy is unacceptable.

Carcinosarcomas of the breast are commonly treated according to the recommendations for epithelial breast cancer as the sarcomatoid differentiation is considered a metaplasia or dedifferentiation of the epithelial tumour cells. These tumours seem to be more chemoresistant compared with intraductal carcinoma of the breast, with a poorer prognosis [53]. Data on the efficacy of adjuvant treatment is sparse, and the optimal treatment paradigm is unknown. RT seems to improve both local control rates and overall survival, and should be considered following lumpectomy or following mastectomy in patients with risk factors such as large tumour (≥ 5 cm) and multiple positive axillary lymph nodes [54]. Biomolecular research to detect differences between epithelial and metaplastic/sarcomatoid breast cancer may reveal novel targets for chemotherapeutic agents to improve outcome in these patients.

- *Head and neck sarcoma:*

STS situated in the head and neck (H&N) area are basically treated according to the same principles and protocols as other bone- and soft tissue sarcomas, depending on histological subtype.
Taking into account availability for superior fixation using a thermoplastic mask, and because of the close proximity to critical normal tissue (eye, lens, optic nerve CNS), the set-up margins may be tighter compared with extremity or trunk location. Hence, a PTV margin of 3-5 mm may be sufficient [55].
A preoperative setting may be advocated in the H&N-region as this entails smaller volumes and lower doses compared with postoperative RT, which is of particular interest due to the close proximity to critical structures [56].

2.2.4 *Hyperthermia, chemotherapy and RT in locally advanced STS*

A randomized study conducted by the EORTC with Haukeland University Hospital as a participating centre, comparing pre- and postoperative thermo- chemotherapy (etoposide, ifosfamide and doxorubicin, 4 courses before and after surgery) with chemotherapy alone in high-risk STS demonstrated improved disease-free survival and local recurrence-free survival in the hyperthermia arm [57]. Furthermore, overall survival was superior in the experimental arm in the group of patients who completed the neo-adjuvant phase.

After conclusion of the EORTC-study, a pilot study of neo-adjuvant three- modality treatment with hyperthermia, chemotherapy and radiotherapy was established at the Centre for bone- and soft tissue tumours, Bergen. The study is open for SSG patients. Inclusion criteria are similar to SSG XX Group B, namely locally advanced soft tissue sarcoma with an obvious risk of intralesional surgery, or in cases where amputation or mutilating surgery is considered necessary to obtain a complete resection of the tumour. Primary or recurrent STS are eligible. In addition to extremity and trunk wall location, tumours located in the pelvis or retroperitoneum may be included if heating of the tumour area is considered feasible. The treatment schedule comprises three courses (3 weeks interval) of doxorubicin and ifosfamide concomitant with regional hyperthermia, followed by trimodal treatment with radiotherapy (1.8 – 2 Gy per fraction to 45-50 Gy over 5 weeks) with weekly hyperthermia and concomitant ifosfamide (Figure 3). The patients will be hospitalised for a week for every thermo-chemotherapy course, and once weekly (2 days) during the 5 weeks of trimodal treatment for the administration of hyperthermia, while staying at the hospital hotel as an outpatient for the radiation treatment days.

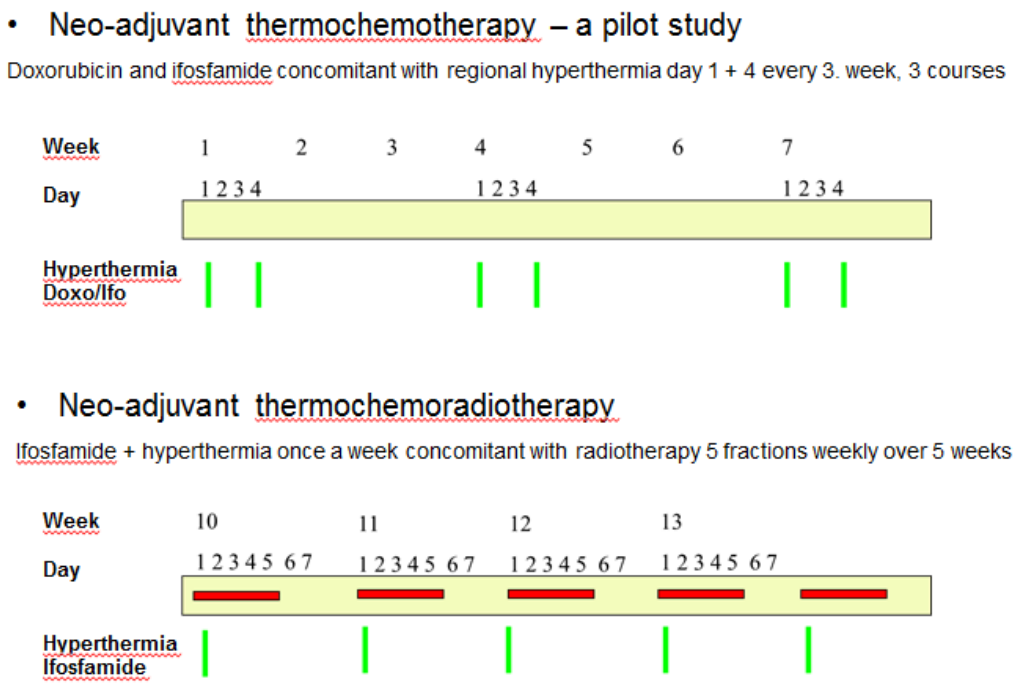

Figure 4. Pilot study on neo-adjuvant trimodal treatment with chemotherapy, radiotherapy and regional hyperthermia in locally advanced soft tissue sarcoma.

3 Bone sarcoma

3.1 *General considerations*

Patients with bone sarcoma are with few exceptions treated according to international or Scandinavian clinical trials or recommendations. The protocols may be considered standard of care, and usually include detailed guidelines for radiotherapy. The median age at the diagnosis of the two most common subtypes of bone sarcoma – osteosarcoma and Ewing's sarcoma, is 15-17 years [58-61]. Most treatment protocols include paediatric patients and young adults. Age > 40 is a negative prognostic factor, however, the prognosis in adult patients improves when adequately treated according to intensive multi-modality programmes [62, 63]. Consequently, all age groups are included in this chapter of bone sarcoma treatment. Proton therapy (chapter 8) and brachytherapy (section 4.4) may have a place in local treatment of young patients with either bone- or soft tissue sarcoma, and these techniques are described separately.

In lack of explicit guidelines for the specification of treatment prescriptions, the principles for target volume definitions in section 1.2 will be applicable also in bone sarcoma. The recommendation for the CTV-margin in bone tissue is 2 cm in the axial direction, and 4 - 5 cm in the longitudinal direction in extremity lesions (long bones). A PTV margin of 0.5 – 1.0 cm is then added, depending on the accurateness of the fixation devise. Verification of patient set up during treatment may be in according to institutional practice.

In children, a particular concern is the growth inhibiting potential of radiotherapy, obliging great care in the planning process of local irradiation.

When a bone sarcoma is located close to central nervous structures, such as tumours of the skull base or cervical spine, proton therapy may be advantageous (see chapter 8).

3.2 *Ewing's sarcoma*

Ewing's sarcoma is considered radiosensitive, and RT plays an important role in the multimodality treatment protocols, either in combination with surgery, or as definitive local treatment in unresectable cases. As for STS, the margin status is predictive of local failure [64, 65]. The choice of local treatment modality is determined by tumour resectability. Surgery alone is recommended whenever feasible, and is preferred in extremity tumours in which adequate surgical margins may be obtained. A combined strategy is often applied in marginally resectable tumours, whereas RT alone is typically used in axially located Ewing's sarcoma and when the tumour is deemed surgically unresectable. Preoperative treatment may be indicated in case of tumour progression, or anticipated inadequate surgical margins. As randomized data are lacking, it is unclear which local approach is optimal. Overall survival seems comparable regardless of local treatment; nonetheless, a higher risk of local failure has been reported with RT alone [66, 67]. However, in unfavourable cases of centrally located tumours, RT is reported to be an effective modality for local control [68].

Inverse planning with IMRT technique may enhance the therapeutic ratio in pelvic Ewing's tumours by improving conformity [69]. A concern in this young patient population is a potential higher risk of secondary malignancies due to the dose bath effect (higher volumes irradiated to low doses in multi-field IMRT-plans). It is important to note that the toxicity of radiation following Busulfan/Melphalan high-dose chemotherapy may be severe, and that such high-dose therapy should be omitted if RT is mandatory and involves unacceptable doses (> 30 Gy) to critical organs such as the central nerve system or brain (Ewing 2008). Equally, Actinomycin D may enhance radiation toxicity, and should on no occasion be administered concomitantly with RT although permitted prior to or after completion of the radiation treatment.

RT in adult Ewing's sarcoma patients is conducted according to the principles in Protocol ISG/SSG III (Treatment protocol for non-metastatic Ewing's family tumours) and Protocol ISG/SSG IV (Treatment protocol for high-risk Ewing's family tumours) (available at www.ssg-org.net), which entail hyper-fractionated accelerated RT concomitant with chemotherapy in order to reduce total treatment time and reduce long-term sequelae by lowering both the fraction dose and total dose. Paediatric patients are treated in concurrence with the above mentioned protocols, or according to the European intergroup randomised trial Ewing 2008 (registered at ClinicalTrials.gov, NCT00987636), depending on institutional preferences. (The multicentre randomised controlled trial Euro-Ewing 2012 is not implemented in Scandinavia, and comprises no recommendations for RT. It is therefore not referred to in this document.)

Data on survival after treatment in consonance with the ISG/SSGIII protocol represents a substantial improvement compared to previous Scandinavian studies. Among the 56 Scandinavian patients included in ISG/SSG III, the 5-year sarcoma related survival was 88% for good responders and 86% for poor responders (the latter receiving high-dose chemotherapy). In total17% of the patients received RT as the definitive local treatment (including the only patient experiencing a local recurrence), 44% underwent surgery alone, and the remaining a combination of surgery an RT (Acta Orthop. suppl. 334, 2009) [70]. In 102 patients included in the ISG/SSG IV (limited metastatic disease), RT was the only local therapy in 20% of the limb tumours, and in 52% of cases with axial primary tumour site. Overall 18 patients experienced local failure [71].

ISG/SSG-protocols III and IV:

RT is given in one series concomitant with chemotherapy. The total dose is tailored to histological response, surgical margin and whether RT is given in conjunction with surgery or as the sole local treatment. Hyper-fractionated accelerated RT is scheduled in the protocol, however, in tumours close to CNS-structures, daily fractions of 1.8 Gy is often preferred.

For non-metastatic tumours, RT is indicated:

1. Following marginal surgery showing viable tumour in the surgical specimen (Picci tumour response I or II)
2. After intralesional surgery
3. In unresectable Ewing's sarcoma.

RT is not indicated after a radical or wide resection, or, following a marginal resection if the surgical specimen shows no viable tumour cells (Picci tumour response grade III).

Adjuvant RT may be indicated for metastatic lesions in the bone following the same principles as for the primary tumour, or, as definitive local treatment in unresectable lesions.

Total lung irradiation is indicated in cases of complete remission of lung metastases after full recovery from the toxicity of high-dose chemotherapy. Surgery of persisting lung nodules may be supplemented. Local RT to persistent nodules is an option if the treatment volume is below 25% of the total lung volume.

The hyper-fractionated accelerated schedule comprises two daily fractions of 1.5 Gy each, and an inter-fraction interval of no less than 6 hours.
Using the equation below, applying an αβ-ratio of 10 Gy for acute effects, and 3 Gy for late responding tissue, the biologically effective doses (BED_{acute}) and late (BED_{late}) effects has been calculated for the different schedules (with a correction factor for total treatment time regarding acute effects), see Table 7.

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) + D_{prolif}(T - T_k)$$

Acute effects (with correction factor for total treatment time)

d	*D*	*a/b*	*T*	*Tk*	*Dprolif*	*BED*	*«EQD2»*
1,8	50,4	10	39	0	0,6	36,1	46,0
1,8	59,4	10	46	0	0,6	42,5	54,0
1,5	42	10	19	0	0,6	36,9	48,0
1,5	54	10	25	0	0,6	47,1	60,0

Late effects

d	*D*	*a/b*	*T*	*Tk*	*Dprolif*	*BED*	*EQD2*
1,8	50,4	3	39	0	0	80,6	48,4
1,8	59,4	3	46	0	0	95,0	57,0
1,5	42	3	39	0	0	63,0	37,8
1,5	54	3	46	0	0	81,0	48,6

Table 7. Calculated BED for the different accelerated schedules in the ISG/SSG protocols for Ewing's sarcoma. The corresponding EQD2-values have been included, but should be interpreted with care, especially regarding early effects. The value for proliferation time (Dprolif) is generically produced, and is not specific/accurate in sarcoma tissue.

The target volumes according to the ISG/SSG protocols are defined from diagnostic radiographs (GTV), with an additional CTV margin of 2-5 cm depending on tumour site and adjacent structures. In doses > 42 Gy, the restricted boost volume should encompass the residual tumour at the start of RT with a CTV margin of 2 cm. Special concerns are necessary in the spine and epiphyseal area. For further details on target volumes and dose to critical organs, see protocols ISG/SSG III and ISG/SSG IV (ssg-org.net) and Table 3 & 4, section 1.2.6.

Ewing 2008:

RT is administered following induction chemotherapy according to treatment arm. In patients receiving high-dose chemotherapy, RT is typically administered 8-10 weeks after reinfusion of stem cells.

In localised disease, preoperative irradiation may be applied to a dose of 54 Gy/1.8 Gy per fraction, 5 days a week, or, as hyper-fractionated accelerated RT to 54.5 Gy, (1.6 Gy twice daily with at least 6 hours interval) to achieve a shorter duration of radiation treatment. Postoperative RT is administered depending on margin and histological response to a dose of 45 -54 Gy in 1.8 Gy fractions. An additional boost to a total dose of 60 Gy may be considered. In case of definitive RT, 45 Gy should be applied to the involved compartment and at least 54 Gy to the tumour, with a boost dose in selected cases; or reduced dose in younger children with complete response to chemotherapy. Normo-fractionated RT with single doses of 1.8 – 2.0 Gy is preferred, but hyper-fractionated accelerated RT (1.6 Gy twice daily with 6 hours interval between each fraction) may be an alternative if normal tissue tolerance allows this approach).

Note: Actinomycin D should be omitted during central axis irradiation.

Whole lung irradiation is delivered to patients with pulmonary metastases at diagnosis to a dose of 15 – 18 Gy (depending on the patient's age) with fraction doses of 1.5 Gy daily, or 1.25 Gy twice daily.

Generally, the tumour extent at diagnosis should be used to delineate the GTV, including scars from biopsy or tumour resection. A shrinking field technique is recommended in patients receiving a boost. According to Ewing 2008, the safety margins should reach 3 - 5 cm longitudinally and 2 cm laterally in extremity tumours (avoid epiphyseal plates if possible). Smaller margins may be applied in tumours of the trunk or head and neck. In chest wall or pelvic lesions, only the residual tumour (non-infiltrating areas) with a safety margin of approximately 2 cm is necessary. For more details regarding target volume definition, see Ewing 2008, Amendment 04 – 1 Aug 2013.

Recommendation Ewing's sarcoma, ISG/SSG III and IV:

Resectable disease:
Following marginal surgery showing viable tumour in the surgical specimen: 1.5 Gy x 2 daily/28 fractions to 42 Gy
After intralesional surgery: 1.5 Gy x 2 daily/28 - 36 fractions to a total dose of 42 - 54 Gy depending of histological response.

Unresectable disease, definitive RT:
1.5 Gy x 2 daily/36 fractions to 54 Gy

Metastatic disease:
Similar indications and doses for metastatic lesions in the bone (definitive or adjuvant).

Total lung irradiation: 1.5 Gy in 10 daily fractions to 15 Gy
Additional RT dose in persistent nodules in the lung (to < 25% of TLV): 1.8 Gy in 14 daily fractions to 25.2 Gy

Recommendation Ewing 2008:

Resectable disease:
Preoperative irradiation to 54 Gy/1.8 Gy per fraction, 5 days a week, or hyper-fractionated accelerated RT to 54.5 Gy, (1.6 Gy twice daily with at least 6 hours interval).
Postoperative RT (depending on margin and histological response): 45 -54 Gy in 1.8 Gy fractions. Boost to 60 Gy in selected cases.

Unresectable disease, definitive RT:
45 Gy to the involved compartment and at least 54 Gy to the tumour, fraction doses of 1.8 – 2.0 Gy is preferred, but hyper-fractionated accelerated may be an alternative.

Metastatic disease to the lung:
Whole lung irradiation in pulmonary metastatic disease at diagnosis to a dose of 15 – 18 Gy with fraction doses of 1.5 Gy daily, or 1.25 Gy twice daily.

3.3 *Osteosarcoma*

Surgery is the mainstay of local treatment in osteosarcoma patients, aiming at wide margins and preservation of function. RT is reserved for cases of involved margin surgery [72, 73]. Osteosarcoma is regarded a relatively radioresistant tumour entity, and a higher RT dose is usually recommended compared with Ewing's sarcoma or STS. The RT dose is tailored to the quality of the surgical margin.

Osteosarcoma patients ≤ 40 years are treated according to Euramos 1, and patients older than 40 years according to Euroboss 1 (www.ssg-org.net).

The recommended dose is in the range of 56-62 Gy following microscopically contaminated margins, and 64-70 Gy when macroscopic tumour tissue is left behind. The dose per fraction should in osteosarcoma probably not be less than 1.8 Gy because of the relative radioresistace in osteosarcoma.

In medically or technically unresectable osteosarcoma, definitive treatment with RT is recommended as local therapy aiming at total doses of at least 70 Gy.
Institutional preferences may include intraoperative electron boost irradiation or brachytherapy high-dose rate after loading techniques to areas of macroscopic residuals.

RT in osteosarcoma should not interrupt or lead to reduction of overall dose-intensity of chemotherapy; rather it should be deferred until the end of chemotherapy.

Protons can improve conformation and sparing of vulnerable tissue (see section 8). In selected cases, proton therapy may allow higher doses resulting in a superior tumour control probability compared with conventional fractionated photon therapy. Hence, proton therapy should be considered in adult osteosarcoma patients when the tumour is located in close proximity to the central nervous system [74]. Furthermore, since the OAR sparing could substantial, proton should be considered in most paediatric patients, even to adjuvant dose levels as clinical studies indicate fewer side effects, including less secondary malignancies. Carbon ion therapy should be mentioned as an alternative option, in particular in unresectable tumours juxta positioned to the central nerve system [75].

According to Euramos 1, the GTV represents all gross tumour volume demonstrable on diagnostic images. Collaboration with a radiologist is encouraged when delineating the GTV. The CTV should be defined in cooperation with the treating surgeon. A 2 cm margin in the axial direction of the affected bone should be attempted, or even up to 5 cm in extremity osteosarcoma. An additional PTV margin of 0.5 – 1.0 cm is advocated, taking into account organ movements and set-up margins.

Recommendation osteosarcoma:

Adjuvant RT: 56-62 Gy in 1.8-2.0 Gy fractions following microscopically involved margins, and 64-70 Gy (1.8-2.0 Gy /fraction) following macroscopically involved resection margins.

Definitive RT is indicated in unresectable osteosarcoma to higher doses ≥70Gy or more with 1.8-2.0 Gy per fraction.

Proton therapy should be considered in most paediatric patients, or in adult patients with unresectable tumours of for instance the skull base or spine.

3.4 *Chondrosarcoma*

Chondrosarcoma are typically slow-growing tumours and empirically considered relatively radio-resistant. The growth pattern is locally invasive, however, they rarely metastasise. Surgery is the key component of multidisciplinary management; however, the typically central localisation of these tumours often precludes complete surgical excision. The risk of local recurrence is correlated with the histological grade. Additional RT effectively prevents local recurrence [76]. Adjuvant systemic therapy is reserved for de-differentiated chondrosarcomas, which are eligible for the Euroboss 1 study (see osteosarcoma). Following inadequate surgery with contaminated margins, or in unresectable tumours, RT to relatively high doses is usually recommended. Because of a likely dose-response relationship, the minimum dose should be 60 Gy, but higher doses up to 70 Gy or more are favoured [77].The dose per fraction is typically

2 Gy, and should be no less than 1.8 because of the relative radio-resistancy of chondrosarcomas. Planned tumour debulking, without trying to obtain complete tumour resection in order to avoid unacceptable surgery-related morbidity, may sometimes be advised to facilitate radiotherapy without compromising otherwise dose-limiting OAR's (e.g. optic chiasm). Following debulking, the volume of the residual tumour correlates with the outcome [78, 79].

Different RT techniques are reported to have comparable efficacy in long-term studies [80]. For unresectable or inadequately resected chondrosarcoma in close proximity to the central nervous system/spinal medulla, promising local control rates with proton therapy has been reported in studies including chondrosarcomas of the skull base or cervical spine [81, 82] (see also chapter 8). Carbon ion therapy is another intriguing approach showing promising local control rates and low toxicity in skull base chondrosarcomas [83].

Recommendation chondrosarcoma:

Adjuvant RT is recommended following inadequate surgery of grade 2-3 chondrosarcoma, and may be considered in grade 1 tumours following incomplete surgery.

Euroboss 1:
Adjuvant 56-62 Gy (1.8 - 2.0 Gy per fraction) following microscopic contaminated surgery, and 64-70 Gy after macroscopic intralesional resection margins.
Definitive RT to 70 Gy or more (1.8 - 2.0 Gy per fraction) in unresectable tumours.

Particle therapy may be considered in unresectable tumours of the skull base or spine.

3.5 *Chordoma*

Chordomas are believed to occur from remnants of the notochord, and are consequentially located along the spine; with sacrum and skull base as the most frequent sites. The proliferation rate is usually slow with an invasive growth pattern. In contrast to most chondrosarcomas, chordomas have a potential for metastasising [84]. RT improves local control, and may be used as adjuvant treatment, or in unresectable tumours [85]. Similarly to chondrosarcoma, the dose to macroscopic disease should reach 64 Gy or more, using a fraction dose of 1.8 – 2.0 Gy. Photon beam therapy combined with surgery results in high local control rates, correlated to the volume of residual tumour following incomplete resection [78].

In chordoma of the skull base or upper cervical spine, evidence exists for the efficacy of dose escalation allowed by applying proton therapy [86, 87] (see chapter 8, Particle therapy).

Recommendation chordoma:

Adjuvant RT may be considered following intralesional surgery to relative high doses of ≥ 64 Gy in 1.8-2.0 Gy daily fractions.

In unresectable chordomas, a dose of up to 70 Gy in 1.8-2.0 Gy daily fractions is most often used.

Proton therapy should be considered, particularly in chordomas of the skull base or upper cervical spine.

4 Radiotherapy in paediatric sarcoma

4.1 *General considerations*

Sarcomas in paediatric patients should always be treated according to international recommendations/protocols.

European recommendations for the treatment of paediatric or adolescent soft tissue sarcomas are encompassed by the EpSSG, European paediatric Soft Tissue Sarcoma Study Group protocols: EpSSG RMS (localised rhabdomyosarcoma) and NRSTS (non-rhabdo soft tissue sarcoma) of 2005, and RMS-MET (metastatic rhabdomyosarcoma) of 2008, or the 2014 "CWS-guidance for risk-adapted treatment of soft tissue sarcoma and soft tissue tumours in children, adolescents, and young adults" by the Cooperative Weichteilsarkom Study Group CWS der GPOH. Detailed recommendations concerning the indications and application of radiotherapy are presented in these guidelines, of which the highlights are summarised in the current document.

Osteosarcoma in children is currently treated according to the Euramos 1 protocol (see section 3.3), standard arm.

Ewing's sarcoma treatment (see section 3.2) follows the Italian-Scandinavian recommendations included in the ISG/SSG III and IV protocols (www. ssg-org.net), or the European study Ewing 2008 (registered at ClinicalTrials.gov, NCT00987636).

As mentioned previously, the growth inhibiting potential of radiotherapy must be taken into careful consideration to avoid unnecessary growth retardation or post-radiation asymmetry of bones.

4.2 *Soft tissue sarcoma*

RT in paediatric STS is normally incorporated in multimodality treatment programmes often including systemic chemotherapy, to improve survival of childhood sarcoma patients [88-91]. Although RT is required in most cases of adult STS, the indications are somewhat less extensive in children because of the considerable higher risk of radiation morbidity, and the use of RT depend on clinical risk factors [90, 91]. Typically, the dose level in treatment of paediatric sarcomas is lower (approximately 50 Gy or less) compared with in adult STS (50-64 Gy). A fraction dose of 1.8 Gy is frequently recommended; or even lower doses (1.6 Gy) in children < 3 years of age.

Rhabdomyosarcoma

Rhabdomyosarcoma is considered a radiosensitive subtype of STS. Multimodality treatment typically includes radiotherapy concomitant with the systemic chemotherapy. According to the EpSSG and CWS-guidance protocols, adjuvant (postoperative) doses of 36 – 50.4 Gy to the primary tumour and regional lymph node metastases is recommended depending on subtype of RMS and the quality of the surgical margin/IRS-group. For instance, RT is advocated after complete resection with negative margins only in patients with alveolar RMS to a total dose of

41.4 Gy in 23 fractions. RT is indicated irrespective of subtype of RMS following resection with microscopic residual disease. The total dose (ranging from 36 – 50.4 Gy) is correlated to subtype of RMS and response to chemotherapy. In cases of macroscopic residual disease, a secondary resection should be undertaken whenever feasible, else, RT is mandatory. In large tumours responding poorly to chemotherapy, an additional boost of 5.4 Gy in 3 fractions may be considered.

According to the CWS-protocol, exceptions to the above mention dose-fractionation are allowed for special sites such as vaginal or orbital location, or in children < 3 years of age. Malignant lymph node involvement without radical lymph node dissection motivates adjuvant RT to a total dose of 41.4 Gy.

Non-RMS tumours

In non-rhabdomyosarcoma tumours in children, the radiosensitivity is highly variable and RT is used to a lesser extent. The EpSSG NRSTS Protocol recommends RT in adult type STS and synovial sarcoma, depending on tumour size and, grade, response to systemic chemotherapy and surgical margin/IRS-group to dose levels of 50.4-54 Gy in the adjuvant setting, or 59.4 Gy with definitive RT. Chemotherapy is often administered concomitant with the postoperative RT.

The CWS-guidance endorse that radiosensitive STS subtypes or “RMS-like tumours” such as synovial sarcoma, soft tissue Ewing tumours (including pPNET), and undifferentiated sarcoma, should principally be treated similar to RMS, although preoperative RT is strongly recommended in order to restrict the irradiation fields. No RT is needed following primary R0 resection. Microscopically or macroscopically residual disease necessitates doses of 50.4 – 54 Gy in 28 or 30 fractions, depending on margin status. Boost doses of 5.4 Gy is optional in case of poor response or progressive disease during chemotherapy. Hyperfractionated accelerated RT with 44.8 Gy, 2 x 1.6 Gy/day according to the previous CWS-recommendations may be an alternative.

For adult type STS or “Non-RMS-like tumours”, the CWS-guidance advocates RT in all standard risk and high risk groups, preferably in the preoperative setting in patients with good/complete response to chemotherapy. Doses of 50.4 – 54 Gy in 28 or 30 fractions are recommended, or alternatively hyperfractionated accelerated RT with 44.8 Gy, 2 x 1.6 Gy/day.

Advanced disease

In the metastatic setting, RT may be used in combination with surgery to improve local control after marginal resections, or in the preoperative setting to improve resectability. Furthermore, RT is applicable in tumour localisations where surgical resection may not be feasible (bone metastases, disseminated central nervous affection).

RT techniques

Photon therapy by megavoltage equipment is usually applied. Electrons may be preferable in superficial located tumours in case of boost. IMRT and tomotherapy may improve conformity reducing dose to critical structures, however, the multiple fields and high dose scatter may be associated with an increased risk of secondary malignancies. Proton therapy allows a high level of conformity as well as producing a steep dose gradient towards critical structures. The technique may be indicated in certain cases (see also chapter 8), typically when the target is located in close proximity to the brain or in cases of paraspinal location, close proximity to the kidneys or intestine, and in pelvic tumours. In moving targets (lung, chest wall, mediastinum, upper abdomen), proton therapy is usually not superior due to technical restrictions. The active scanning techniques are preferred before passive scattering as the latter theoretically

may entail a higher risk of secondary cancer. However, overall, proton treatment allows less scattering of the dose, which might reduce the risk of secondary cancer compared with photon based techniques. For a second opinion on proton therapy, the Scandion Clinic in Uppsala, can be contacted. Cyberknife treatment and stereotactic RT are highly focused small field techniques reserved for small targets. Brachytherapy is useful for instance in incompletely resected tumours of the pelvis or head- and neck region (see below – section 4.4).

Target volumes and Normal Tissue Tolerance

The GTV may preferably be defined based on MRI images of the initial tumour. The CTV encompass the GTV + an additional margin of typically 1 cm (2 cm in longitudinal direction in the limbs), in addition to scars or potentially contaminated tissues during surgery. To delineate the PTV, an additional margin of 5 – 10 mm should be defined (2 cm for chest wall). Further restriction of the volumes (pertaining to total dose levels) is described in the current paediatric studies, as well as recommendations for maximum tolerated doses to critical structures.

4.3 *Bone sarcoma*

The incidence of the most frequent types of bone sarcoma is higher among younger patients compared to middle aged or older adults. Most protocols include children and adults (typically up to 40 years). Chapter 3 comprise information on current treatment protocols for both paediatric and adult bone sarcoma patients, which are only briefly referred to below. Brachytherapy is a valuable radiation treatment option typically applied in children and young adults when tumours are located in close proximity to critical structures such as the central nervous system or sense organs. The indications and technique is described in a subsection of this chapter.

The guidelines for RT in the Euramos 1 (section 3.3) are consultative for RT of paediatric osteosarcoma. Osteosarcoma is considered a relatively radioresistant entity, and RT is restrained to cases of inadequate surgical margins or surgically unresectable tumours. Palliative RT may also be an option in metastatic disease.

Ewing's sarcoma is particularly radiosensitive compared with other bone sarcomas. Ewing 2008 and the Italian/Scandinavian treatment programmes ISG/SSG III for non-metastatic Ewing's family tumours and ISG/SSG IV for high-risk Ewing's family tumours (see www/ssg-org.net) comprise guidelines for RT (see section 3.2), which is regularly applied as a component of multi-modality treatment in non-wide resections or in unresectable tumours. RT is also frequently used in lung metastases or bone metastases from Ewing's sarcoma.

According to the ISG/SSG protocols, the RT is administered in a hyper-fractionated accelerated design with two daily fractions to total doses of 42-54 Gy, depending on the quality of the surgical margin, and the histological/radiological response after induction chemotherapy. Metastatic lesions may be treated to similar doses as the primary tumour. Following complete remission of lung metastases, a total of 15 Gy in 10 fractions is administered adjuvant to the total lung volume. Alternatively, a dose of 25.2 Gy (1.8 Gy x 14) may be targeted to viable lung lesions if the total irradiated volume comprises less than 25% of the total lung volume.

4.4 *Brachytherapy*

According to CWS-guidance, in cases of incomplete resected tumours located in the vagina, perineum, bladder or prostate, or in tumours of the head- and neck area, brachytherapy may be an option – either as a boost combined with external beam radiation, or as a replacement for external beam RT. Ref? In patients included in the CWS-guidance study, this should be discussed with the CWS Study Centre. Individual dosage is calculated taking into account the tumour location and adjacent critical structures.

Similarly, brachytherapy is proposed in Euramos 1 as an option in the local treatment of osteosarcoma.

Karolinska University Hospital in Stockholm has experience with brachytherapy in paediatric patients. Also, the University Clinic Schleswig-Holstein in Lübeck, and the Gustave Roussy Institute of Oncology, Villejuif, Paris, offer brachytherapy to children and adolescents.

4.5 *Normal tissue tolerance guidelines*

Generally, normal tissue tolerance guidelines are included in the clinical studies/treatment protocols for the different sarcoma subtypes. In paediatric patients, extra care must be taken to avoid RT dose to critical structures as the risk of late effects is higher and the patients have a longer lifespan during which radiation morbidity may develop. Secondary cancer is another major concern. An increased risk of a secondary cancer exists also in lower doses to normal tissue, hence the concern that IMRT may entail an increased risk of a potentially harmful bath dose. In contrast, proton treatment entails less scattering of the dose, theoretically reducing the risk of secondary cancer compared with conventional photon based techniques.

Recommendation paediatric sarcoma:

RT guidelines in specific paediatric protocols for the treatment of bone and soft tissue sarcoma in children and young adults should be followed.

5 Radiotherapy in abdominal sarcoma

SSG recommendations for treatment of intra-abdominal, pelvic and retroperitoneal sarcoma were updated in 2008 (SSG XVII, www.ssg-org.net). There is lack of international consensus concerning adjuvant radiotherapy in sarcoma of these localisations. In SSG XVII, it is acknowledged that radiotherapy may be considered following intralesional resection of an intra-abdominal sarcoma. A prerequisite is that the surgeon could avoid contamination of the peritoneal cavity during surgery. In addition, radiotherapy may serve as the sole local "definitive" treatment in unresectable tumours (also see section 2.2.3). The dose has to be restricted relative to the OAR limitations of intra-abdominal organs, and the treatment must therefore be considered palliative. Hypo-fractionated treatment with 3 Gy fractions is an option in the palliative setting.

The Norwegian Radium Hospital, Oslo University Hospital, and Karolinska Hospital, Stockholm are participating centres in the ongoing EORTS multicentre study in which preoperative radiotherapy in retroperitoneal sarcoma is investigated (STRASS study). Patients are randomized to undergo neo-adjuvant radiotherapy prior to en-bloc resection, or surgery alone. Patients with resectable, unifocal, non-metastatic sarcoma of the retroperitoneum, including infraperitoneal sarcoma of the pelvis, are eligible and should be assessed for inclusion. Potential study participants are referred to the investigating centres in SSG (Oslo and KS) for evaluation. Both the radiotherapy and the surgical procedure will be undertaken at the hospitals approved by the EORTC for this study.

Recommendation abdominal sarcoma (also see section 2.2.3):

The Scandinavian Sarcoma Group (SSG) recommends participation in the currently running EORTC randomised clinical trial investigating preoperative RT versus surgery alone for resectable RPS.

Adjuvant RT may else be considered following individual assessment in patients with retroperitoneal tumours of malignancy grades 3-4 and macroscopic or microscopic positive surgical margin.

An adjuvant dose of 50 Gy in 1.8 – 2.0 Gy fractions is typically applied, which may be reinforced with a boost of up to 10 Gy in areas of macroscopic positive surgical margins.

In unresectable intra-abdominal sarcoma, RT to 50 – 60 Gy (or more if feasible) Gy in 1.8 – 2.0 Gy fractions may be an option.

Palliative RT, preferably hypofractionated (3 Gy x 10-12 or 4 Gy x 5), may be an option to relieve local symptoms from abdominal lesions – whether they represent primary tumours or metastatic manifestations.

6 Radiotherapy in gynaecological sarcoma

Uterine sarcoma may occur in all age groups, and include leiomyosarcoma and endometrial stromal sarcoma. In addition, mixed tumours (carsinosarcoma and adenosarcoma) may occur in the uterus. Carsinosarcomas are considered metaplastic endometrial carsinomas and are treated accordingly.

There is a lack of evidence that adjuvant radiotherapy improves the disease free survival in gynaecological sarcoma, hence, radiotherapy is not routinely recommended in this tumour entity [92, 93]. The SSG Recommendations for treatment of intra-abdominal, pelvic and retroperitoneal sarcoma (SSG XVII) (see www.ssg-org.net) reflects this. However, favourable local control following adjuvant pelvic RT has been reported [94-96], and adjuvant RT is for instance advocated in the ESMO guidelines (2013) following surgery of localised (stage II-IVA) high-grade uterine sarcoma [97]. Adjuvant RT in uterine sarcoma may therefore be discussed on an individual basis in multi-disciplinary meetings.

Radiotherapy may be considered in local advanced tumours that are not amenable for surgery, taking into account the tumour site and feasibility of radiotherapy in the particular location.

Recommendation gynaecological sarcoma:

In the adjuvant setting, RT may be considered on an individual basis.

In unresectable uterine sarcoma, RT to 50 – 60 Gy (or more if feasible) Gy in 1.8 – 2.0 Gy fractions may be an option.

Palliative RT, preferably hypofractionated (3 Gy x 10-12 or 4 Gy x 5), may be an option to relieve local symptoms in advanced disease.

7 Radiation induced sarcoma

A serious late effect of irradiation is the development of a secondary sarcoma within the radiation field. The latency period is long (median 8-14 years) [98-101] and should be at least 2 years with no signs of sarcoma prior to RT to classify as a secondary sarcoma. Furthermore, a radiation induced tumour must present as a different histopathological entity than the primary tumour. Radiation induced sarcoma comprise 2.5-5.5% of all sarcomas [98, 102]. The most common types of primary tumours previously irradiated when patients later presents with an in-field sarcoma are retinoblastoma, breast carcinoma, gynaecological cancers, testicular cancer and malignant lymphoma [99, 100, 102]. Radiation induced sarcoma often presents as undifferentiated pleomorphic sarcoma, angiosarcoma, osteosarcoma or MPNST [100]. The prognosis is poor unless a complete surgical resection is obtained [99, 102]. Adjuvant RT seems beneficial also in radiation induced sarcoma [101].

Treatment of a radiation induced sarcoma should follow the same principles as for sporadic sarcomas, adjusting the radiation dose according to previous irradiation and overlap. There is limited clinical data concerning the tolerance of re-irradiation, and the reluctance for applying yet another series of RT to the same target volume is often high as the risk of late-effects will increase with increasing RT dose. In different solid tumours, adjuvant re-irradiation in the setting of a local recurrence is reported to be effective and feasible, with brachytherapy as an interesting option [103-105]. There is no consensus as to which RT dose is acceptable in re-irradiation [106]. Doses equivalent to 60-80% of the original biologically effectively dose are considered to be well tolerated [107]. A repair factor of 33% is typically used if the time lag from end of primary RT to re-irradiation is minimum 6 months, also taking into account recorded late-effects of previous the treatment course. The re-irradiation dose is also determined by the total dose of and the interval since the initial irradiation; the dissimilar ability of involved tissues to recover from previous irradiation; as well as other factors delaying recovery (comorbidity, age, chemotherapy, age etc.). A cumulative dose of maximum 160% of tolerance dose is suggested. The patient has to be thoroughly informed about the increased risk for complications.

Recommendation radiation induced sarcoma:

The tumours should be treated in keeping with the guidelines for sporadic sarcoma.

The RT dose should be adjusted according to the previous irradiation dose.

8 Proton therapy

No randomised studies compare particle therapy with photons in sarcoma treatment. Based on available evidence, the American Society of Radiation Oncology (ASTRO) concluded in 2012 that proton therapy seemed superior in chordomas, paediatric central nervous system tumours and in large ocular melanomas [108]. In children in particular, when late effects of radiotherapy is of great concern, proton therapy may reduce the risk of late morbidity, including secondary cancers [109]. The radiobiological and physical principles of improved conformity and sparing of normal tissue with protons have been presented as an argument for implementing particle therapy without the requisition of positive phase III studies [110]. The rarity of sarcoma underscores this argument. However, data displaying clinical benefits of particle therapy in sarcoma treatment have been published.

Proton therapy seems to be valuable in chordoma, and in particular chordoma of the skull base, as this enables dose escalation and hereby increases the probability of local tumour control [86, 87]. Good local control accompanied by limited treatment-related morbidity has been reported in studies including both chordomas and chondrosarcomas of the skull base or cervical spine [81, 82]. Promising results are seen also in unresectable or incompletely resected bone tumours such as osteosarcoma and Ewing's sarcoma [74, 111]. Dose distribution studies have demonstrated superior conformity parallel with improved shielding of normal tissue in paediatric patients with orbital rhabdomyosarcoma and pelvine sarcoma, in addition to intra-abdominal and paraspinal soft tissue sarcoma [112-115].

Particle therapy utilising heavy ions is more experimental. However, reports on carbon ion therapy demonstrate effect on tumour control with moderate toxicity in bone- and soft tissue sarcoma of various localizations [75, 116].

The rationale to favour particle therapy (in practical protons) before photon therapy in sarcoma patients is based on the potential of improved curability following definitive radiotherapy to high doses in relative radioresistant, primary bone sarcomas inaccessible for surgical resection. Bone sarcoma of the skull base is thought to be the foremost indication for proton therapy. Patients with primary bone tumours or soft tissue sarcoma with close proximity to critical structures of the central nerve system may be considered for particle therapy if required total target dose is high. In patients with Ewing's sarcoma of which local cure by definite radiotherapy is achieved with total a dose of 54 Gy, the advantage of particle therapy is less pronounced. However, since the OAR sparing is substantial, proton therapy should be considered in most paediatric sarcoma patients to reduce the risk of late effects and secondary cancers.

When proton therapy may be indicated, it is recommended that the responsible oncologist discuss the case with radiation oncologists familiar with proton therapy, for instance radiation oncologists at the Skandion Clinic in Uppsala, Sweden. For second opinion on proton therapy at the Scandion clinic in Uppsala, radiotherapy departments at the University hospitals in Lund, Gothenburg, Linköping, Stockholm, Uppsala, Örebro or Umeå may be contacted.

Proton therapy should be considered in:

Bone sarcoma (chordoma, chondrosarcoma, osteosarcoma) of the skull base.

Sarcoma of bone or soft tissue in which a high RT dose is required within a volume of close proximity to critical structures such as the central nervous system.

In paediatric patients, regardless of dose, when substantial sparing of organs at risk is deemed necessary (i.e. in most paediatric sarcoma patients with centrally located tumours).

9 Palliative radiotherapy

In palliative settings, radiotherapy is an important approach to relieve local symptoms such as pain and delay tumour growth. Choice of fractionation should be applied in accordance with institutional practice. Late morbidity is of less concern in these instances, and higher fraction doses are therefore usually recommended to shorten the total treatment time.

However, in patients with localised but unresectable tumours, definitive RT to high doses (≥ 70 Gy) may be indicated. Standard fractionated RT (50 Gy /25 fractions) may be applied in symptomatic metastases (pain, bleeding etc.) situated in close proximity to vulnerable structures (intestines, CNS etc.) in patients with a good performance status and with a reasonable life expectancy.

The typical fractionation schedule is 3 Gy x 10 [117]. Doses up to 3 Gy x 12-15 may be considered in patients with slowly progressing disease or a relative long expected life span, depending on tumour size and expected dose to adjacent organs-at-risk. In cases of instant need for palliation in patients with a short life expectancy, 4 Gy x 5 (during 5 consecutive days) is a less time consuming schedule. In relieving pain from bone metastases, 8 Gy x 1 is the preferred choice based on several recent phase 3 trials, meta-analyses and a Cochrane review [118, 119]. There is, however, less evidence for the efficacy of single fractionation in bone metastases from sarcoma compared with metastases from carcinomas. Single fraction RT may be repeated if local symptoms recur. Although single fraction in bone metastases is reported to have the same effect on pain compared with multiple fractions, the duration of the effect may be shorter and re-irradiation more often needed [120]. Hence, the patient's life expectancy and institutional RT resources should be taken into consideration when deciding on the fractionation schedule in palliative treatment of sarcoma.

Recommendation palliative RT:

Hypo-fractionated treatment with 3 Gy x 10 -15 or 4 Gy x 5.

Single-, or oligometastases in the lung(s) may be treated with stereotactic technique (SBRT) to for instance 45 Gy in 3-5 fractions depending on proximity to large vessels or central bronchial tree.

Single fraction of 8 Gy in bone metastases may be considered.

10 Toxicity and follow-up

Acute or early toxicity manifest < 90 days after the last radiation treatment fraction, and may be dose-limiting in severe cases. Erythema of the skin is expected, and may progress into desquamation or necrosis. Oedema may affect the involved limb, and wound complications or an increased risk of infections is reported when radiotherapy is administered prior to surgery [20]. Radiation enteritis with spasms and diarrhoea is a potential risk when intestines are included in the target volume. Early effects are reversible – often within 1-2 weeks following termination of RT, and do not necessarily correlate with the risk of developing late morbidity.

In the treatment phase, the irradiated skin areas should be kept dry and protected against mechanical irritation. Daily (x 2-3) application of saline moist dressing for 20 minutes may relieve local skin symptoms. Radiation enteritis may be alleviated with dietary measures, and nausea treated with antiemetic drugs. In severe cases, it may be necessary to interrupt the radiation treatment. In extremity tumours, prophylactic physiotherapy should be initiated to avoid development of contractures.
Late morbidity may occur months to years after the treatment (per definition at least 90 days after the completion of the last fraction). The most common signs are fibrosis of the skin and subcutaneous tissue, contractures of skin and joints, and oedema [30]. More seldom osteoporosis of involved bone, osteoradionecrosis or pathological bone fractures may follow RT [121]. Secondary cancers and retarded growth of involved organs is a major concern in paediatric patients, and hormonal status must be monitored when the radiation volume involves hormonal glands. In severe cases, late morbidity may compromise physical function, the ability to participate in daily life activities and health related quality of quality of life [21, 22].

Late effects may reach a plateau, slowly improve or gradually progress over time.

The different organs/normal tissues have varying sensitivity and volume dependence to RT. Dose-volume constraints should follow documented tolerance limitations, for instance the QUANTEC recommendations [7].

Tolerance is reduced when radiotherapy is administered in close relation or concomitant with chemotherapy [40, 122]. Simultaneous use of drugs such as doxorubicin or actinomycin D with RT should be avoided, and these drugs should be used with precaution also after the completion of RT.

Follow up after multimodality treatment of sarcomas should include an examination of the irradiated area, and recording of the highest observed morbidity grade. Radiation morbidity may be categorised and reported according to the EORTC/RTOG radiation morbidity scoring scale [123].

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Mayo 2018 – SARCOMA DE EWING FÉMUR

1.- DESCRIPCIÓN DEL CASO

Paciente de 15 años con sarcoma de Ewing en fémur derecho (con afectación de vasto interno, 120x50x30 mm).
Tras QT neoadyuvante se interviene con resección amplia y colocación de megaprótesis.
El resultado A-P muestra necrosis del 40%. Bordes libres
Se decide RT adyuvante. Según protocolo SEOP 2001 se indican 48 Gy (36 + 12)

2.- DUDA CONSULTADA

Las preguntas son:

- ¿Utilizáis hiperfraccionamiento?
- ¿Se debe incluir la cicatriz aunque en este caso está en la parte externa del muslo, lo que amplía bastante el CTV?
- ¿Utilizáis bolus para que la cicatriz?
- En el Euro Ewing 2012 no hay cambios en la RT. ¿Alguien tiene otro protocolo más actualizado?

3.- RESPUESTAS

➢ El Euro Ewing 2012 es el protocolo más reciente de tratamiento. Entiendo que este paciente está realizando la QT según este protocolo, y la indicación de RT es, obviamente, por la pobre respuesta a la QT.

En cuanto a las dudas que planteas:

- El hiperfraccionamiento ya no está contemplado en este protocolo, no ha demostrado ser superior al normofraccionamiento. Por tanto, se trataría normofraccionada a una dosis total de 54 Gy en 30fr (PTV1: 45 Gy + PTV2: 9 Gy).

- Los volúmenes de tratamiento los decides tú. Verás que respecto a las prótesis y la cicatriz el protocolo ya especifica

que NO es necesario incluirlas en toda la extensión si eso aumenta el volumen de tratamiento mucho y por tanto la toxicidad. Yo no pongo bolus en cicatriz si no había infiltración de piel al diagnóstico ni incluyo toda la cicatriz si la cirugía ha sido oncológica y sin roturas que pudieran contaminar el campo quirúrgico.

- En cuanto a la técnica, yo utilizaría IMRT. En extremidades ayuda a preservar más tejido sano de la extremidad para evitar toxicidades tardías (fibrosis de tejidos blandos, y no sé si cogerás los cartílagos de crecimiento de los huesos largos, aunque la paciente tenga 15 años hay que ver si están ya cerradas las fisis o no). Dra. M. Ramos Albiac

➢ Comparto todo lo que ha comentado la compañera. Último protocolo EuroEwing 2012. Yo haría exactamente lo mismo que ella. Dra. Sonia García

➢ También utilizo el EuroEwing 2012. Dra. Elena Arregui

➢ Nada que añadir a lo que ha comentado Mónica. Totalmente de acuerdo. Dr. Raúl Matute

➢ En mi último caso aplique el protocolo que comenta la Dra. Ramos y sin problemas Dr. José Luis Pérez Aguiar

➢ Estoy de acuerdo con lo que ha comentado Mónica. El tema más conflictivo sería la inclusión de la cicatriz en el volumen de tratamiento. Hay que tener en cuenta que aunque el Sarcoma de Ewing es un "*sarcoma*" es un tumor emparentado con los tumores PNET al igual que el Rabdomiosarcoma, y la tendencia es incluir la cicatriz en el volumen de tratamiento, sobre todo si "no cuesta nada", pero es un tumor claramente diferenciado de los sarcomas, los cuales no hay duda al respecto. La verdad es que la evidencia de incluirla es débil. En "*The Cooperative Ewing's Sarcoma Studies (CESS) 81 and 86 and the European Intergroup Ewing's Sarcoma Study 92*" incluyendo 1058 pacientes no se menciona para nada la inclusión de la cicatriz en el volumen de tratamiento, de lo cual se deduce que la inclusión no fue obligatoria. En otros artículos donde se recomienda, si sigues la bibliografía verás que no esto está tan claro el tema, se repiten las citas....Envío un artículo de revisión

donde se responde a las preguntas, protocolo de grupo escandinavo de 2015 y este último artículo que comento. Dr. Claudio Fuentes Sánchez

4.- CONCLUSIÓN

Siguiendo el protocolo Euro Ewing 2012, el paciente tiene indicación de Radioterapia postoperatoria por la pobre respuesta a la QT neoadyuvante (necrosis del 40 %)

El tratamiento con Radioterapia seria normofraccionada a una dosis total de 54 Gy en 30 fracciones de 1,8 Gy /fracción (PTV1: 45 Gy + PTV2: 9 Gy) dado que el hiperfraccionamiento no ha demostrado ser superior al normofraccionamiento.

La inclusión de la cicatriz en el volumen de tratamiento no sería preciso si aumenta la toxicidad de este. Este es el punto de mayor controversia, aunque la evidencia a favor de la inclusión es débil.

Se debería incluir la cicatriz y valorar la colocación de bolus, cuando hay infiltración de piel al diagnóstico, si la cirugía no ha sido oncológica y si ha habido roturas que pudieran contaminar el campo quirúrgico.

Si es posible utilizar IMRT para evitar fibrosis de tejidos blandos y preservar los cartílagos de crecimiento de los huesos largos

5.- BIBLIOGRAFÍA