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Radiotherapy of localized soft tissue sarcoma

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Content

Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer.

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the ”Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations”, https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.
Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website: https://www.sst.dk

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1. Anbefalinger - DA (Quick Guide)

Indikationer

1. **Radioterapi kombineret med ekstremitets bevarende kirurgi med vid eller marginal margin er standard behandling af lokaliserede dybt liggende højmalignt sarkomer (A).**

2. **Radioterapi bør udelades efter operation med vid eller marginal margen i lavmaæignt sarkomer (A).**

3. **Radioterapi bør udelades efter operation med vid margin i overfladiske (subkutane) sarkomer uanset grad (B).**

4. **Radioterapi er ikke en erstatning for genoperation i højmalignt sarkomer med positiv (intralesional) margen (B), men kan brugs for lavmalignt sarkom (B).**

5. **Udvalgte dybdeliggende sarkom særlig dem der er under 5 cm i diameter kan behandles alene med kirurgi, hvis margenen var >1 cm (B).**

6. **Radikal strålebehandling bør overvejes til radikal behandling i kliniske situationer, hvor ingen acceptabel kirurgisk behandling er tilgængelig (B).**

Timing og interval

7. **Radioterapi kan gives enten præ- eller post- operativt (A).**

8. **Hvis re-eksicion er planlagt, kan radioterapi gives enten præ- eller postoperativt (B).**

9. **Ved præoperativ strålbehandling, skal det ikke tilføjes en boost efter operationen, hvis margenerne var marginale eller intralæsionelt (B)**

10. **I tilfælde af positiv margen efter præoperativ stråleterapi kan yderligere onkologisk behandling vurderes i henhold til den estimerede risiko for recidiv (MS).**

11. **Det optimale interval mellem kirurgi og strålebehandling (enten præ- eller post-operativt) er 3-6 uger (A).**

12. **Den maksimale forsinkelse tilladt før den postoperative strålebehandling er 4 måneder (B).**

Dosis og fraktionering

13. **Patienter, der modtager præoperativ stråleterapi, bør behandles med 50 Gy i 2 Gy / fraktion som standrad præoperativ dosis (A).**

14. **Patienter, der modtager postoperativ stråleterapi, bør behandles med en minimumsdosis på 50 Gy i 2 Gy / fraktion + A boost til tumorlejet op til 66 Gy afhængige af den kirurgiske margenstatus (B).**

15. **Patienter, der behandles med radikal-intenderet strålebehandling, bør behandles med 68-74 Gy givet med 1,8 - 2,0 Gy daglige fraktioner (B).**

16. **Alternativ fraktionering (accelererede, hypofraktionerede eller accelererede hyperfraktionerede regimer) er ikke standard, men kan anvendes i udvalgte tilfælde (B).**

Target definition

17. **Target for præoperativ strålebehandling bør afgrænses som følger: 1) Gross target volumen (GTV) defineres ved hjælp af T1-vægtet MR med kontrast. 2) kliniske target volumen (CTV) er konstrueret ved at udvide GTV 3,5 - 4 cm i længderetningen og 1,5 cm lateralt og forfra-bagfra retning. CTV bør omfatte peritumeralt ødem på T2-vægtede scanninger, men bør ikke udvides ud over overfladen af de tilstødende knogler og fasciae, medmindre disse strukturer er involverede (A).**

18. **Target for postoperativ strålebehandling bør afgrænses som følger: 1) CTV'en forlænges i alle retninger med 1,5 cm, undtagen i længderetningen, hvor udvidelsen er 4 cm. Radialt bør det elektive CTV omfatte arret og enhver postoperativ væskeopsamling, men behøver ikke udvides længere end huden og overfladen af de tilstødende knogler, fasciae og leddene, medmindre disse strukturer er involveret. 2) Boostet er det samme volumen som det elektive CTV, undtagen i længderetningen, hvor det er defineret af den rekonstruerede GTV plus en 2 cm-margin (A).**

19. **Target for radikal strålebehandling bør defineres som følgende: 1) GTV defineres af den T1-vægtede MR med kontrast. 2)CTV er konstrueret ved at udvide GTV 3,5-4 cm i længderetningen og 1,5 cm lateralt og forfra-bagfra retningr. CTV bør omfatte**

peritumeralt ødem på T2-vejede scanninger, men bør ikke udvides ud over overfladen af de tilstødende knogler og fasciae, medmindre disse strukturer er involveret. 3) Boost CTV er GTV plus en 2 cm margen i længdeplanet, men den radiale margen er 0,5 -1,0 cm (A).

Teknik

20. **Sarkomapatienter bør behandles med intensitetsmoduleret strålebehandling (IMRT) teknik, mens billedstyret radioterapi (IGRT) teknik anbefales, når den er muligt og relevant (B).**

Site-specifik strålebehandling

21. **For retroperitoneal og intra-abdominal sarkomer, kirurgi er standardbehandling (A).**

22. **For retroperitoneale og intra-abdominale sarkomer, bør præoperativ stråleterapi overvejes inden for kliniske forsøg, men både adjuverende strålebehandling (50 Gy i ± boost op til 10 Gy) og radikal strålebehandling (≥ 60 Gy) kan overvejes i udvalgte tilfælde (C).**

23. **For uterin sarkomer, kirurgi er standardbehandling (A).**

24. **For uterin sarkomer, kan adjuverende strålebehandling (50-60 Gy) overvejes i udvalgte tilfælde (B).**

25. **Standardbehandling for hoved og hals sarkomer er kirurgi + postoperativ stråleterapi (60-66 Gy), men præoperativ strålebehandling kan overvejes til individuelle patienter (B).**

26. **Radioterapi bør overvejes i højmalignt bryst sarkomepatienter der opereres med marginalmargin og hos patienter med intralesionale marginer, hvis der ikke kan udføres re-eksicion (B).**

Histologisk specifik strålebehandling

27. **Patienter med rhabdomyosarcoma bør behandles i overensstemmelse med resultaterne af den seneste europæiske rhabdomyosarkom protokol (EpSSG, 2005) som beskrevet i bilag 3 (A).**

Proton behandling

28. **Børn og unge voksne patienter, der modtager højdosis radioterapi til blødedel sarkom på kritiske steder som hoved og hals, paraspinal region, bækken og bases cranii bør overvejes for Proton-terapi (B).**

1. Recommendations - ENG (Quick Guide)

Indications

1. **Radiotherapy combined with limb sparing surgery with wide or marginal margin is treatment of choice for localized deep seated high grade sarcomas (A).**
2. **Radiotherapy is omitted after surgery with wide or marginal margin in low grade sarcomas (A).**
3. **Radiotherapy is omitted after surgery with wide margin in superficial (subcutaneous) sarcomas regardless of grade (B).**
4. **Radiotherapy is not a substitute for re-excision in high grade sarcomas with positive (intralesional) margin (B) but optional for low-grade sarcomas (B).**
5. **Selected deep seated intermediate/high grade sarcomas particularly those < 5cm in diameter could be treated with surgery alone if the margin was wider than 1cm (B).**
6. **Radical radiotherapy should be considered for radical treatment in clinical situations where no acceptable surgical option is available (B).**

Timing and interval

7. **Radiotherapy can be given either pre op post operatively (A).**
8. **If re-excision is planned, radiotherapy can be planned either pre or postoperatively (B).**
9. **If preoperative radiotherapy is used, do not add boost after surgery if the margins were marginal or positive (B).**
10. **In case of positive margin after preoperative radiotherapy additional oncologic treatment could be considered according to the estimated risk of recurrence (MS).**
11. **The optimal interval between surgery and radiotherapy (whether pre or postoperative) is 3-6 weeks (A).**
12. **The maximum delay allowed for the post-operative radiotherapy is 4 months (B).**

Dose and fractionation

13. **Patients receiving preoperative radiotherapy should be treated with 50 Gy in 2 Gy/fraction as the standrad preoperative dose (A).**

14. **Patients receiving postoperative radiotherapy should be treated with a minimum dose of 50 Gy in 2 Gy/ fraction + A boost to the tumour bed up to 66 Gy according to the surgical margin status (B).**

15. **Patients treated with definitive radiotherapy should receive a dose of 68-74 Gy given with 1.8 - 2.0 Gy daily fractions (B).**

16. **Alternative fractionation (e.g. accelerated, hypofractionated or accelerated hyperfractionated regimens) is not standard but can be used in selected cases (B).**

Target definition

17. **Target for preoperative radiotherapy should be delineated as following: 1) The gross tumor volume (GTV) is defined using gadolinium-enhanced, T1-weighted MRI, 2) The clinical target volume (CTV) is constructed by expanding the GTV 3.5 – 4 cm longitudinally and 1.5 cm laterally and antero-posteriorly. CTV should include peritumeral edema on T2-weighted scans but should not be expanded beyond the surface of the adjacent bones and fasciae, unless these structures are involved (A).**

18. **Target for postoperative radiotherapy should be delineated as following: 1) The CTV is extended in all directions by 1.5 cm, except longitudinally, where the expansion is 4 cm. Radially, the elective CTV should include the scar and any postoperative fluid collection but does not need to be expanded further than the skin and the surface of the adjacent bones, fasciae, and joints, unless these structures are involved.** 2) **The boost is the same volume as the elective CTV, except in the longitudinal direction, where it is defined by the reconstructed GTV, plus a 2 cm margin (A).**

19. **Target for radical radiotherapy should be delineated as following: 1) The GTV is defined by the gadolinium-enhanced, T1-weighted MRI, 2) The clinical target volume (CTV) is constructed by expanding the GTV 3.5 – 4 cm longitudinally and 1.5 cm laterally and antero-posteriorly. CTV should include peritumeral edema on T2-weigted scans but should not be expanded beyond the surface of the adjacent bones and fasciae, unless these structures are involved. 3) The boost CTV is the GTV plus a 2 cm margin in the longitudinal plane, but the radial margin is 0.5 -1.0 cm (A).**

Technique

20. Sarcoma patients should be treated with intensity modulated radiotherapy (IMRT) technique and image guided radiotherapy (IGRT) technique is recommended when feasible and relevant (B).

Site specific radiotherapy

21. Standard treatment for retroperitoneal and intra-abdominal sarcomas is surgery alone (A).

22. For retroperitoneal and intra-abdominal sarcomas, preoperative radiotherapy should be considered within clinical trials but adjuvant radiotherapy (50 Gy ± a boost of up to 10 Gy), or radical radiotherapy (≥ 60 Gy) can be considered in selected cases (C).

23. Standard treatment for uterine sarcomas is surgery alone (A).

24. For uterine sarcomas, adjuvant radiotherapy (50-60 Gy) can be considered in selected cases (B).

25. **Standard treatment for head and neck STS is surgery + post-operative radiotherapy (60 -66 Gy) but preoperative radiotherapy can be considered for individual patients (B).**

26. **Radiotherapy should be considered in high grade breast sarcoma patients operated with marginal margin and in patients with intralesional margins if re-excision cannot be performed (B).**

Histology specific radiotherapy

27. **Patients with rhabdomyosarcoma should be treated according to the results of the most recent European rhabdomyosarcoma protocol (EpSSG, 2005) as detailed in appendix 3 (A)**.

Proton therapy

28. **Children and young adult patients receiving high dose radiotherapy for soft tissue sarcomas in critical sites such as the head and neck, paraspinal region, pelvis and base of skull should be considered for Proton therapy (B).**

2. Introduction

Surgery using amputation has always been the main line of treatment for localized soft tissue sarcoma (SST) yielding local control rates of >80% (1). Some non-randomized (2) and an early single randomized study (3) showed that limb sparing surgery (LSS) + post-operative radiotherapy is as effective as amputation in terms of local control and survival. Thus, establishing this treatment as the golden standard of localized SST in the last 3 decades. The challenge in sarcomas is their rarity, and distribution between various histological subtypes and anatomical localizations. Most of the studies and randomized trials in sarcomas are being done in the trunk and extremities. The experiences gained in these sites are being extrapolated for treating sarcomas in other sites and the practice is later confirmed by various retrospective and single institution studies.

This guideline examines the evidence that has been accumulated regarding the role of external beam radiotherapy in treating sarcomas. The recommendations are based on the expected effect on local control rate and possibly overall survival.

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.

The specific objective is to describe the details of applying radiotherapy in patients with localized soft tissue sarcomas. These details include: indications, timing and interval, dose and fractionation, target definition, techniques, site specific and histology specific radiotherapy as well as the evidence of using proton therapy. The guideline is also concerned with specifying the various subgroups in which radiotherapy could/should be omitted.

Target population

All adult patients with localized soft tissue sarcoma treated with radical intent regardless of grade and anatomical site.

Target User

This guideline is developed to support clinical decision-making and quality improvement. Thus the target users are healthcare professionals working in Danish cancer care.

3. Scientific evidence

Indications

1. **Radiotherapy combined with limb sparing surgery with wide or marginal margin is treatment of choice for localized deep seated high grade sarcomas (A).**

2. **Radiotherapy is omitted after surgery with wide or marginal margin in low grade sarcomas (A).**

3. **Radiotherapy is omitted after surgery with wide margin in superficial (subcutaneous) sarcomas regardless of grade (B).**

4. **Radiotherapy is not a substitute for re-excision in high grade sarcomas with positive (intralesional) margin (B) but optional for low-grade sarcomas (B).**

5. **Selected small deep seated intermediate/high grade sarcomas particularly those tumours ≤ 5cm in diameter could be treated with surgery alone if the margin was wider than 1cm (B).**

6. **Radical radiotherapy should be considered for radical treatment in clinical situations where no acceptable surgical option is available (B).**

Literature review and evidence description

Deep seated high grade sarcomas

The evidence for the indication of radiotherapy in deep seated high grade sarcomas comes from two randomized studies (4, 5) [1b] with two subsequent long term follow up publications (6, 7) [1b] showing that limited limb sparing surgery combined with adjuvant radiotherapy is superior to surgery alone. One of these two trials used adjuvant external beam radiotherapy (141 patients) and the other used adjuvant brachytherapy (164 patients). In both trials combined therapy significantly increased local control rate for high grade but not for low grade sarcomas. Moreover, both trials showed no increases in the overall survival rate.

Further evidence is derived from two major retrospective studies (8, 9) [2b, 2c]. The first is a French study on 3255 soft tissue sarcoma patients showing that adjuvant radiotherapy was associated with a significant benefit in terms of local relapse-free survival despite a higher incidence of competing deaths in patients managed with adjuvant radiotherapy compared to patients not receiving radiotherapy (8) [2b]. The other large study was a Scandinavian database analysis of adjuvant radiotherapy in a 1093 adult patients with extremity or trunk wall soft tissue sarcoma treated in the period 1986–2005. The study confirmed that adjuvant radiotherapy reduced the risk of local recurrence in soft tissue sarcoma, irrespective of the tumor depth, malignancy grade, and surgical margin status (9) [2c]. The most evident reduction however was in deep seated high grade sarcomas.

The local control results are summarized in table 1.

		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 1. 5-year local control rates by prognostic group and radiotherapy in 1093 patients with extremity and trunk wall soft tissue sarcoma (9). Red colour denotes statistical significance, blue is borderline significant and black is no significance.

Based on Yang et al. og Beane et al. (3, 4) [1b], as well as the most recent European School of Medical Oncology (ESMO) guidelines (10), and other reviews (11), the strength of the recommendation for radiotherapy of deep seated high-grade sarcomas is evaluated to be strength A.

Low grade sarcomas
The same prospective and retrospective studies had a subgroup of low grade sarcomas and their analysis showed that radiotherapy could be safely omitted for low grade sarcomas operated wide or marginal margin surgery as both local control rates and long term overall survival after surgery alone are excellent (4-7) [1b], (8) [2c], (9)[2c].

Based on the prospective trials (4-7) [1b], the 2 large retrospective analysis (8) [2c], (9) [2c] as well as the most recent ESMO guidelines (10), the strength of the recommendation for radiotherapy of deep seated low-grade sarcomas is estimated to be strength A.

Superficial (subcutaneous) sarcomas
There is no randomized trial studying radiotherapy in superficial (subcutaneous) sarcomas. The evidence regarding the indication for radiotherapy in this disease category was derived from 3 retrospective studies (9, 11, 12)[2c].

The first comprised 129 patients with subcutaneous sarcoma diagnosed between 1964-1985 in Sweden, and showed that only 7% of the high-grade tumors recurred locally after wide local excision without radiotherapy

(11) [2c]. The second study reported results from 622 consecutive, surgically treated superficial soft tissue sarcoma patients that were treated with surgery and selective radiotherapy. The incidence of local recurrence and metastasis was 9% and 12%, respectively. Factors that affected survival and local recurrence were tumor size, age and tumor grade. Clear surgical margins were correlated to lower risk for local recurrence and selected patients benefited from adjuvant radiotherapy. The authors concluded that surgery with adequate surgical margins is adequate, whereas radiotherapy has a secondary role and may be used in selected patients (12) [2b]. The third study is the Scandinavian database study mentioned earlier (9) [2c] and summarized in table 1. It confirmed that surgery with wide margin alone is optimal treatment enough for superficial sarcomas with 86% 5-year local control rate. The study showed however that surgery alone is not satisfactory if the margins were less than wide and confirmed the value of adjuvant radiotherapy in improving local control rate in these cases.

Based on the retrospective studies (9) [2c], (11, 12) [2b], and other reviews (13-15)[2b] the recommendation for radiotherapy of superficial sarcomas is estimated to be strength B.

Intralesional margin
The evidence for the indication of radiotherapy following surgery yielding intralesional margin is derived from the large database Scandinavian study (9) [2c] and a retrospective study of 110 adult patients with primary high-grade extremity STS who underwent limb sparing surgery and were found to have a histologically positive microscopic surgical margin (16) [2b]. In both studies radiotherapy significantly improved the local control rate compared to the no radiotherapy group. The local control however was inferior to that achieved in patients with wide or marginal margin (17) [2b]. Radiotherapy can't be considered a substitute for re-excision in positive margin (intralesional excision) high grade sarcomas.

The evidence based on these 2 studies (9) [2c], (17) [2b] and ESMO guidelines (10)[2c] is considered to be strength B.

Radiotherapy also improved local control for low grade sarcomas after inadequate surgery. This was shown in the large Scandinavian database study (9) [2c] as well as in a small retrospective analysis of 132 patients with low grade sarcomas (18) [2b]. Radiotherapy however is associated with known late effects (19) [2b]. The low risk of metastasis means that the decision to give radiotherapy has to be weighed against late effects of radiotherapy.

The evidence based on these 2 studies (9) [2c], (18) [2b] is considered to be strength B.

T1 (< 5 cm) deep seated intermediate/high grade sarcomas
The evidence for radiotherapy in this subgroup comes from 3 studies (20-22) [2b,2c,2b]. The first study describe a long term follow up study of a prospective trial testing surgery alone in 88 patients with STS of trunk and extremities. Subgroup analysis of patients with small tumours (T1) and R0 resection showed a cumulative incidence rates of local recurrence at 5 and 10 years of 7.9% and 10.6%, respectively; and a 5- and 10-year sarcoma-specific death rates of 3.2% and 3.2% (16) [2b]. The second study was a large SEER database study of 983 patients showing better survival for patients with sarcomas >5cm in diameter receiving adjuvant radiotherapy but no survival difference for patients with tumours < 5cm (17) [2c]. The third study describe a

retrospective analysis of 204 patients with small (≤5cm) STS tumours of the extremeties where 88 received post operative radiotherapy using brachytherapy technique and 116 did not. There was no difference in local control or survival between the two groups (18) [2b].

The evidence based on these 3 studies (20) [2b],(21) [2c], (21) [2b] is considered to be strength B.

Radical radiotherapy
In case of inoperable sarcomas, the use of radical radiotherapy was tested in many retrospective studies using photons or proton therapy. The various studies have consistently showed local control rates of 25-50% depending on the tumour size and grade (22, 23) [2b].

Based on these 2 retrospective studies (23, 24) [2b] and ESMO guidelines (10) [2c] the strength of evidence for the use of radical radiotherapy in inoperable sarcomas is considered to be strength B. As there can never be a study randomizing between radiotherapy and no treatment it is considered a standard of care.

Patient values and preferences
In case of sarcomas in the extremities, the historical alternative to this recommendation is amputation. We assume that the majority of patients would prefer a limb preserving surgery and radiotherapy over amputation.

Rationale
The outcome that forms the basis of the recommendation is local control, limb preservation, better limb function and a good quality of life. The current recommendation does not only preserve the limb but also a good function. This is balanced against amputation (in case of extremity sarcoma) or major mutilating surgery in case of sarcoma to other sites.

Timing and interval

7. **Radiotherapy can be given either pre op post operatively (A).**
8. **If re-excision is planned, radiotherapy can be planned either pre or postoperatively (B).**
9. **If preoperative radiotherapy is used, do not add boost after surgery if the margins were marginal or positive (B).**
10. **In case of positive margin after preoperative radiotherapy additional oncologic treatment could be considered according to the estimated risk of recurrence (MS).**
11. **The optimal interval between surgery and radiotherapy (whether pre or postoperative) is 3-6 weeks (A).**
12. **The maximum delay allowed for the post-operative radiotherapy is 4 months (B).**

Literature review and evidence description

Pre or postoperative radiotherapy

The best evidence regarding treatment sequencing comes from the Canadian Sarcoma Group's SR2 randomized trial of pre- vs postoperative radiation (25) [1b]. This trial randomly assigned patients with localized primary or recurrent extremity sarcomas to be treated using external-beam radiation (50 Gy with a 16 Gy boost for microscopically positive surgical margins) followed by surgery, or surgery followed by external-beam radiation (66 Gy). This trial with its later long term follow up results (26, 27) [1b] in addition to meta-analysis (28) [2c] and one retrospective study (29) [2b] confirmed that preoperative RT was equivalent to postoperative RT regarding local control and long-term physical function. Sequencing radiotherapy when re-resection is planned was tested in one retrospective study of 249 patients in whom re-excision was planned. The study showed that here was no evidence that radiotherapy sequence influenced local control, metastatic control, disease-free survival, or disease-specific survival between the pre and the postoperative radiotherapy groups (30) [2b].

Based on the prospective trial results (25-27) [1b], that was confirmed by meta-analysis (28) [2c] and retrospective data (29) [2b] and in accordance with the most recent ESMO guidelines (10) the strength of the recommendation for the timing of radiotherapy is evaluated to be strength A.

Value of boost after preoperative radiotherapy

Marginal margin after preoperative radiotherapy doesn't compromise local control (31) [2b]. In an attempt to study the value of postoperative boost for patients receiving preoperative radiotherapy, a retrospective study evaluated patients who received preoperative radiotherapy (n = 49) and patients who received preoperative radiotherapy with a postoperative boost (n = 45). There were no differences in the proportion or rate of local recurrence, distant metastasis or death due to sarcoma between the two groups (32) [2b]. Another retrospective study in 216 patients showed that to be true even if the surgical margin was positive (33) [2b].

Based on the 3 retrospective studies (31-33) [2b], the strength of the recommendation for the boost following preoperative radiotherapy of deep seated high-grade sarcomas is evaluated to be strength B.

Interval

The Canadian prospective randomized study planned surgery 3-6 weeks after the end of preoperative radiotherapy (25) [1b]. The time interval between surgery and postoperative radiotherapy is usually the same (3-6 weeks). Data on the effect of prolonged interval caused by, for example, infection was gathered from 4 studies (34-37). The largest was a database retrospective French study in more than 1000 patients. There was no effect on local control rate or survival of prolonged time up to 4 months between surgery and start of adjuvant radiotherapy (34) [2b]. The same results were seen in 2 other retrospective studies (35, 36) [2b]. The fourth and last retrospective study in 100 patients showed that more than 4 months delay lead to inferior local control rates (37) [2b].

Based on the 4 retrospective studies (34-37) [2b], the strength of the recommendation for the interval between surgery and radiotherapy of deep seated high-grade sarcomas is estimated to be strength B.

Patient values and preferences

Radiation-associated wound complications rate in patients receiving preoperative radiation was about 33% vs 16% in the postoperative radiation arm (25). However, the late tissue effects including fibrosis and edema were more common following postoperative radiation (28, 29). These effects are irreversible and were probably related to the higher radiation dose and larger field size required for postoperative radiation.

Rationale

Tumour regression after preoperative radiotherapy is limited. Preoperative radiotherapy can't be aimed at rendering an inoperable tumour, operable.

Dose and fractionation

13. **Patients receiving preoperative radiotherapy should be treated with 50 Gy in 2 Gy/fraction as the standard preoperative dose (A).**

14. **Patients receiving postoperative radiotherapy should be treated with a minimum dose of 50 Gy in 2 Gy/ fraction + a boost to the tumour bed up to 66 Gy according to the surgical margin status (B).**

15. **Patients treated with definitive radiotherapy should receive a dose of 68-74 Gy given with 1.8 - 2.0 Gy daily fractions (B).**

16. **Alternative fractionation (e.g. accelerated, hypofractionated or accelerated hyperfractionated regimens) is not standard but can be used in selected cases (B).**

Literature review and evidence description

The preoperative dose

The evidence for the current preoperative standard dose of 50Gy in 2 Gy/fx lies in the Canadian prospective study comparing pre vs. postoperative radiotherapy (25) [1b]. In this study the experimental arm was the preoperative radiotherapy and the study proved that 50 Gy is as effective the more established postoperative dose of 60-66 Gy. There are no prospective studies comparing various preoperative doses.

Based on this trial by O'sulivan et al. (25) [1b] and various international guidelines (10, 38-40) [2c,1a-1a] the evidence for the preoperative dose is considered to be strength A.

The postoperative dose

The evidence for the current practice of delivering a dose of 60-66 Gy in the postoperative setting could be traced to an old retrospective study from MD Anderson in which the data of 465 sarcoma patients receiving either pre or postoperative radiotherapy was analyzed. The postoperative dose ranged from 50 to 65 Gy and the data suggested that 50 Gy postoperative is probably not adequate for proper local control (41) [2b]. Contrary results were seen in some more recent retrospective studies from Scandinavian centres (42) [2b] and

from France (43) [2b] showing that post-operative radiation dose of 50 Gy may lead to the same local control rates as other studies delivering higher doses. An explanation to the different results may be in applying strict patient selection criteria and using modern surgical techniques in specialized sarcoma centers.

The only prospective clinical trial on which our current postoperative practice is built was done in 91 patients randomized between 2 arms. Patients in the postoperative radiotherapy arm received 63 Gy to tumour bed and 45 Gy to wider margin (4) [1b].

A large retrospective study in 775 patients with high risk of local recurrence after gross total resection showed that patients with high risk of local recurrence benefited a radiotherapy dose of 64-68 Gy compared to 60 Gy (44) [2b]. The same tendency was described in 2 small earlier retrospective studies (45, 46) [2b]. [A more recent study in 154 patients with positive surgical margin confirmed by multivariate analysis that patients who received doses > 64 Gy had better local control rates (47) [2b].

Based on the only prospective study (4) [1b] and the various retrospective data (41-44) [2b] as well as the various current guidelines (38-40)[1a] the strength of the evidence for the current postoperative dose (50 Gy + risk adapted boost to 66 Gy) is considered to be strength B.

Radical radiotherapy
The evidence for the radical radiotherapy dose is derived from the above mentioned retrospective studies (44-47) [2b] describing a dose-response relationship between the total dose and local control. This relationship suggests that high radiation doses are needed for large inoperable tumours. In radical radiotherapy for inoperable tumours, a standard radiotherapy practice is to deliver doses > 66 Gy leading to a local control rate of 25-50% depending on tumour type and risk factors (23, 24) [2b].

The strength of evidence for the dose for radical radiotherapy in inoperable sarcomas based on these retrospective studies is estimated to be strength B.

Alternative fractionation
Various alternative fractionation (accelerated, hypo-fractionation, hyper-fractionation or split course) were tested in various trials or small single institutions retrospective studies (48-51) [3b]. All studies claimed equal results with standard fractionation but because of the small number of publication and the lack of comparative prospective studies there can be no recommendations of using alternative fractionation outside clinical trials [B].

Patient values and preferences

Hypo-fractionation could be preferred by some patients as the overall treatment time is shorter but the risk of late effects is higher. The value of alternative fractionation should be weighed against possible risks.

Rationale

The current practice and recommendation provide effective local control and an acceptable risk of acute and late effects. Hypo-fractionation may increase late effects while hyper-fractionation is associated with more acute toxicities. In both cases the biological tumour dose should not be compromised. Therefore alternative fractionation is only recommended within clinical trials.

Target definition

17. **Target for preoperative radiotherapy should be delineated as following: 1) The gross tumor volume (GTV) is defined using gadolinium-enhanced, T1-weighted MRI, 2) The clinical target volume (CTV) is constructed by expanding the GTV 3.5 – 4 cm longitudinally and 1.5 cm laterally and antero-posteriorly. CTV should include peritumeral edema on T2-weighted scans but should not be expanded beyond the surface of the adjacent bones and fasciae, unless these structures are involved (A).**

18. **Target for postoperative radiotherapy should be delineated as following: 1) The CTV is extended in all directions by 1.5 cm, except longitudinally, where the expansion is 4 cm. Radially, the elective CTV should include the scar and any postoperative fluid collection but does not need to be expanded further than the skin and the surface of the adjacent bones, fasciae, and joints, unless these structures are involved.** 2) **The boost is the same volume as the elective CTV, except in the longitudinal direction, where it is defined by the reconstructed GTV, plus a 2 cm margin (A).**

19. **Target for radical radiotherapy should be delineated as following: 1) The GTV is defined by the gadolinium-enhanced, T1-weighted MRI, 2) The clinical target volume (CTV) is constructed by expanding the GTV 3.5 – 4 cm longitudinally and 1.5 cm laterally and antero-posteriorly. CTV should include peritumeral edema on T2-weigted scans but should not be expanded beyond the surface of the adjacent bones and fasciae, unless these structures are involved. 3) The boost CTV is the GTV plus a 2 cm margin in the longitudinal plane, but the radial margin is 0.5 -1.0 cm (A).**

Literature review and evidence description

Detailed recommendations for radiotherapy definition for dose planning are missing in the majority of the published data. Old retrospective data on postoperative radiotherapy suggest cranio-caudal margin that is at least 5 cm and < 10 cm (52) [2b]. The evidence for standard target definition in this guideline was based on the NCIC prospective trial comparing pre- and postoperative external beam radiotherapy (25) [1b]. This target definition practice is supported by the optimal local control of 92% in one retrospective study of 56 patients adopting the same guidelines (53) [2b] compared to slightly lower control rate (88%) in another retrospective

study using smaller margins (54) [2b]. Including the postoperative fluid collection in adjuvant radiotherapy is based on one retrospective study of 88 patients of sarcoma in the trunk wall and extremities who received postoperative radiotherapy. The postoperative fluid collection was included in the majority of the patients. After a median follow-up of 4.3 years, patients with and without fluid collection had 5-year local control rates of 77.7% and 90.8% (P = 0.105). Eight patients with fluid collection had local recurrence, of which six patients had recurrent tumors at or within 4 cm of the collection wall suggesting that it could be a risk factor for recurrence (55) [3b].
Various consensus papers and guidelines confirmed the use of the same target for preoperative and postoperative radiotherapy (56-58, 39).
Target definition for radical radiotherapy of sarcomas in the trunk and extremities is similar to the preoperative radiotherapy to the 50Gy volume. The boost to the higher dose is similar in concept to the postoperative boost. However smaller margin to CTV may be needed since the total dose is higher as described in the Scandinavian sarcoma group guidelines (39) and the last rhabdomyosarcoma and non-rhabdomyosarcomas EpSSG protocols that also included adult patients (appendix 3).

Based on the cumulative data from 1 prospective study (25) [1b] and 3 retrospective studies (52-54) [2b), (55) [3b] as well as various guidelines (39) and current protocols describing best standard practice, the strength of evidence for target definition could be considered as strength A.

Patient values and preferences

Not relevant.

Rationale

The current standard practice and recommendations allows for optimal coverage of tumour volume and areas at risk of microscopic disease to reduce the risk of local recurrence and adapt the clinical target volume to the anatomical site and allows for smaller target in areas such as the head and neck.

Technique

20. Sarcoma patients should be treated with intensity modulated radiotherapy (IMRT) technique and image guided radiotherapy (IGRT) technique is recommended when feasible and relevant (B).

Literature review and evidence description

The evidence in this guideline was based on 8 small single-arm and retrospective studies (59-66) [2b,3b, 3b, 2b, 3b, 2b, 2b, 3b] confirming the values of the new technique in line with what is to be expected based on the new technological advancement.

IMRT has been evaluated prospectively in 18 patients and showed that it reduced the severity and incidence of wound healing complications through sparing the uninvolved tissues (59) [3b]. Other reports showed that the better sparing of normal tissue (60-62) [3b,3b,2b] when IMRT was used was associated with better target coverage (63) [3b], and significantly reduced local recurrence compared with conventional external beam

therapy (64) [2b]. One study showed that image guided radiotherapy (IGRT) technique significantly reduced late toxicities after preoperative radiotherapy without increasing marginal-field recurrences (64) [2b]. Another study showed that IGIMRT reduced would complication below expected values and significantly diminished the need for tissue transfer (65) [2b]. In one non-randomized study local control with IMRT was significantly better than brachytherapy despite higher rates of adverse features in the IMRT cohort (66) [3b].

Intensity modulated radiotherapy (IMRT) is a technologically advanced techniques allowing for better dose conformity in tumor target and lower doses to organs at risk. Applying new and better technologies does not always require evidence from randomized clinical trials.

Based on the 8 retrospective studies [3b] that confirmed the value of IMRT, the strength of evidence is considered to be strength B.

Patient values and preferences

Not relevant.

Rationale

IMRT technique seems to able to spare normal tissues from excessive high dose of irradiation without compromising tumour target coverage with optimal radiation dose. Though never tested in prospective clinical trial the current data is in agreement with the expected theoretical benefit and justifies its use as standard.

Site specific radiotherapy

21. Standard treatment for retroperitoneal and intra-abdominal sarcomas is surgery alone (A).

22. For retroperitoneal and intra-abdominal sarcomas, preoperative radiotherapy should be considered within clinical trials but adjuvant radiotherapy (50 Gy in ± a boost of up to 10 Gy), or radical radiotherapy (≥ 60 Gy) can be considered in selected cases (C).

Literature review and evidence description

There is lack of randomized studies and consensus concerning the role of radiotherapy in retroperitoneal sarcoma. The evidence in this guideline is based on retrospective institution-based studies that reported improved local control following pre or post-operative radiotherapy but the numbers of patients are small and the results are conflicting and could be biased (67-72) [2b,2b,2b2b,2b,3b,3b,2b]. EORTC is currently undertaking a multicenter study in which preoperative radiotherapy in retroperitoneal sarcoma is investigated against surgery only (STRASS study). One retrospective study reported a possible improved local control of radical radiotherapy to doses as high as 66 Gy (70) [3c] in inoperable retroperitoneal sarcomas. A population based study in over 2000 patients with non-retroperitoneal abdominal sarcomas, radiotherapy (adjuvant) seemed to improve survival (73) [3b] but the results should be regarded with caution since the majority of confounding factors could not be accounted for.

Based on 6 retrospective studies (67-72) [2b,2b,2b2b,2b,3b,3b,2b] and one database study (73) [2c] that are suffering from possible selection and publication bias the strength of evidence regarding the role of radiotherapy in retroperitoneal and intraabdominal sarcomas is estimated to be strength C.

23. Standard treatment for uterine sarcomas is surgery alone (A).

24. For uterine sarcomas, adjuvant radiotherapy (50-60 Gy) can be considered in selected cases (B).

Literature review and evidence description

The evidence regarding the role of radiotherapy is derived from one randomized trial (74) [1b] and 10 [2c] retrospective studies (75-85) [2b,2c-2c]. The results of the prospective study suffered from the fact that recruited only 224 patients in 13 years and included various sarcoma subtypes. Patients were randomized to either observation or pelvic radiation, 51 Gy in 28 fractions over 5 weeks. The analysis showed a significant reduction in local relapse (p=0.004) in the radiotherapy arm but no effect on survival or progression free survival. The majority of the reported retrospective studies showed favorable local control following postoperative pelvic radiotherapy of localised (stage II-IVA) high-grade uterine sarcoma (75-85) [2b,2c-2c]. The largest study analyzed data from 2206 patients with non-metastatic uterine sarcoma treated with surgery with or without adjuvant radiotherapy (75) [2c]. Adjuvant radiotherapy was delivered as external beam radiation to the pelvis, with or without brachytherapy. The 5-year local recurrence free survival was 87%. Radiotherapy was one of the prognostic factors and was associated with improved local control compared with surgery alone ($p < 0.001$).

Based on the evidence from the prospective study of Reed NS et al. (74) [1b] and the various retrospective studies (75-84) [2b), reviews (85) [2b] and international guidelines (39) [1a], the strength of evidence for the role of radiotherapy in uterine sarcomas is considered to be strength B.

25. Standard treatment for head and neck STS is surgery + post-operative radiotherapy (60 -66 Gy) but preoperative radiotherapy can be considered for individual patients (B).

Literature review and evidence description

It is generally recommended that STS situated in the head and neck (H&N) area be treated according to the same principles and protocols as other bone- and soft tissue sarcomas, depending on histological subtype (39) [1a]. Site-specific radiotherapy considerations regarding fixation and high precision small set-up margins (PTV = 3 - 5 mm) are common practice that is in accordance with treating carcinomas of the H&N (86) [2b]. There are no prospective trials regarding radiotherapy of H&N sarcomas. The evidence on the role of radiotherapy is derived from data base (87) [2c] and 2 retrospective studies (88, 89) [2b], all suggesting that adjuvant post-operative radiotherapy is feasible and may lead to better control and superior survival than surgery alone.

Preoperative radiotherapy entails smaller volumes and lower doses compared with postoperative radiotherapy, and have therefore some advantages for H&N because of the close proximity to critical organs at risk (87, 39) [2c,1a].

In a retrospective study of 40 patients with H&N STS treated with pre-op RT (50 Gy) and subsequent (4 to 6 weeks later) resection, the actuarial 2-year local relapse-free rate was 80% and major wound complications occurred in 8 of 40 patients (20%) within 120 days of surgery (90) [3b]. These results suggested that pre-op radiotherapy in H&N STS is associated with lower rates of major wound complications compared to extremity cases and that it provides high rates of local control in this adverse group of patients (90) [3b]).

26. Radiotherapy should be considered in high grade breast sarcoma patients operated with marginal margin and in patients with intralesional margins if re-excision cannot be performed (B).

Literature review and evidence description

Breast sarcomas can be of various histological subtypes. The most common are Phylloids breast tumours and angiosarcomas. Phylloides tummurs are either benign, borderline or malignant while angiosarcomas can be spontaneous or radiation induced (following irradiation for carcinoma of the breast). Similar to localized STS in other sites, surgery is the main treatment for localized breast sarcomas (39, 40) [1a]. In the majority of breast sarcoma patients, total mastectomy including fasciectomy may be necessary to obtain adequate surgical margins (41). Dissection of the axillary lymph nodes is not routinely performed (39-41) [1a,1a,3b].

The evidence on the role of radiotherapy is derived exclusively from retrospective and database studies (91-100) [2b-2b,3b] since randomized trials are lacking. All studies suggest that, adjuvant postoperative radiotherapy, regardless of histological type, could reduce the risk of local recurrence in high-risk, patients (high grade and/or inadequate margin) without improving survival (91-100) [2b-2b,3b].

Based on these retrospective studies (91-100) [2b] and expert opinion expressed in various guidelines (39-41) [1a-1a,3b] and reviews (14) [2b], the strength of the evidence for the role of radiotherapy in breast sarcoma is evaluated as being strength B.

Patient values and preferences

Not relevant.

Rationale

Sarcomas can affect any site in the body and surgery is the main treatment of localized soft tissue sarcoma regardless of the site. The rationale of adding radiotherapy to the standard surgical intervention is not only to improve local control the disease but to preserve the function of the affected site/organ if possible and avoid mutilating surgical procedures.

Histology specific radiotherapy

27. Patients with rhabdomyosarcoma should be treated according to the results of the most recent European rhabdomyosarcoma protocol (EpSSG, 2005) as detailed in appendix 3 (A).

Literature review and evidence description

There are accumulated evidence from randomized studies that Rhabdomyosarcoma should have specific dosage and indications. Prospective randomized clinical trials lead by international organizations as the European pediatric soft tissue study group (EpSSG) and the German Cooperative Cooperative Soft Tissue Sarcoma Studies (CWS) are defining the standard treatment in most European countries. EpSSG protocols have been the standard of care in Denmark for the last decades. Rhabdomyosarcoma protocols are valid for both children and adults. The current doses and indications are summarized in table I &2 and are drived from 10 publications (101-109) [1b] based on data from the prospective protocols. Detailed radiotherapy description of the most recent EpSSG protocol (EpSSG 2005) is attached in appendix 3 and summarized in the tables below.

Table 1: rhabdomyosarcoma indications and doses

Indication	Risk group	Eberyonal dose & fx	Alveolar Dose & Fx
initial complete resection, no microscopic or macroscopic residual tumour, no lymph node involvement	**I**	**No Rth**	**41.4 Gy; 23 fx.**
grossly resected tumour with microscopic residual disease or evidence of regional lymph node involvement	**II**	**41.4 Gy; 23 fx**	**41.4 Gy; 23 fx**
initial incomplete resection with gross residual disease. Follpwed by secondry complet eresection	**III a**	**36 Gy; 20 fx (if PR)** **41.4 Gy; 23 fx (if SD)**	**41.4 Gy; 23 fx**
initial incomplete resection with gross residual disease followed by incomplete secondry resection	**IIIb**	**50.4 Gy; 23 fx**	**50.4 Gy; 23 fx**
initial incomplete resection with gross residual disease follwoed by clinical CR. No second look operation	**IIIc**	**41.4 Gy; 23 fx**	**50.4 Gy; 23 fx**

initial incomplete resection with gross residual disease followed by PRn NC or PD, no second look operation	**IIId**	**50.4 Gy; 23 fx 0 boost 5.4 Gy; 3fx** **Except orbit & PR 45 Gy; 25fx**	**50.4 Gy; 23 fx + boost 5.4 Gy; 3fx**

Table 2. Radiation dose for the lymph nodes

Situation	**Eberyonal/Alveolar RMS**
No Clinical or pathological involvement of regional nodes	**No Radiotherapy**
Clinically or pathologically positive lymph nodes; excised or in complete remission before radiotherapy	**41.4 Gy; 23 fractions**
Positive Lymph nodes, macroscopical residual disease before radiotherapy	**41.4 Gy; 23 fractions + 9Gy boost in 5 fractons**

Based on the evidence derived from publications based on prospective trials (101-109) [1b], reviews (110) [1b] and best standard of care in international protocol (appendix 3), the strength of evidence for the role of radiotherapy in rhabdomyosarcoma is considered to be strength A.

Patient values and preferences

Not relevant.

Rationale

The current practice according to the most recent EpSSG guidelines is based on a risk stratification strategy that adjusts treatment intensity according to the risk of death from disease and takes into account patients age and the anatomical site of the disease..

Proton therapy

28. Children and young adult patients receiving high dose radiotherapy for soft tissue sarcomas in critical sites such as the head and neck, paraspinal region, pelvis and base of skull should be considered for Proton therapy (B).

Literature review and evidence description

No randomized studies compare particle therapy with photons in sarcoma treatment. The superior dose distribution and improved conformity of protons combined with better sparing of normal tissue have been presented as an argument for implementing particle therapy without positive phase III studies (111) [2b] particularly in rare tumours as sarcomas and in children where the risk of late secondary cancer is of particular concern (112) [c]. The evidence for the value of proton therapy was therefore derived from retrospective studies displaying clinical benefits of particle therapy in primary and recurrent sarcomas in sites such as the head and neck, pelvis/abdomen and paraspinal regions (113-124) [c,c,3b,2b,2b,2b,2b,2b,3b,3b,3b,,2b].

Based on evidence derived only from retrospective studies of small number of patients the strength of evidence for the role of proton therapy in treatment of soft tissue sarcoma is considered to be strength B.

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5. Methods

Literature search

Evidence was looked for in Medline database using “Sarcoma” and “Radiotherapy” as a MESH terms. Details of the search terms are in the appendix (1). The search was restricted to English language human studies in adults. The following studies were excluded:

- Case reports
- Studies with less than 50 patients unless they are unique or providing the only evidence
- Studies with only pediatric population
- Studies describing brachytherapy or intraoperative radiotherapy

We didn’t set a time frame but we ended up excluding most of the old studies dating before 1990 because they used old techniques and usually included few very limited number of patients. The search terms results included reviews and meta-analysis, so we didn’t make specific search for reviews.
A second source of evidence was found in various international guidelines. Guidelines focusing on aspects other than radiotherapy, for example chemotherapy or palliative treatment were excluded.
A third source of evidence was sought in the radiotherapy guidelines in some previous and current international protocols such as the EpSSG rhabdomyosarcoma and nom rhabdomyosarcoma protocols as well as or the EORTC STRASS protocol as well as in the Scandinavian sarcoma group radiotherapy guidelines they are describing the best standard radiotherapy practice. Some essential references in these protocols were retrieved and used (see flow chart, appendix 4).

Evidence assessment

The critical appraisal of the selected evidence was done by the author of the guidelines. The data on the selected radiotherapy parameter for example; dose or fractionation or technique were extracted from the article and measured against the selected outcome. The quality of the evidence depended on the study design and the number of patients as well as the ability of the study to account for possible confounders and modificators. The strength of the recommendations was graded according to the strongest evidence (see evidens table, appendix 5)

Articulation of the recommendations

The recommendation was formulated by the author of the guidelines in the first draft. The formulation will be revised by members of the DSG from various specialties to reach an expert consensus formulation.

Stakeholder involvement

There was no attempt at involving patients in the current guidelines as it was not considered possible.

External review and guideline approval

There was a continuous dialogue with RKKP secretariat during preparation of the guidelines. Feedback from secretariat was included and the guideline was modified accordingly. Members from DSG representing both oncologists and orthopedic surgeons in the 2 national sarcoma centers received and commented the first draft of the guidelines and their comments were incorporated in the final version.

Recommendations which generate increased costs

No additional cost is estimated.

Need for further research

There is a need for further research to elucidate:

1. The value of preoperative radiotherapy, the value of dose escalation using protons, dose contstraints in limb irradiation.

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6. Monitoring

Standards and indicators

The current DSG database include parameters and indicators that would help monitoring the adherence to the guidelines. The database include data on which patients received radiotherapy and various radiotherapy indicators such as timing, date, dose and fractionation. From these data one can calculate other parameters such as dose per fraction and overall treatment time. The database includes registration of acute and late radiation-related side effects and their severity grade.

Plan for audit and feedback

The guideline has been, while under preparation, revised by members from the 2 national sarcoma centers. It will be presented to the remaining members of the DSG during the next meeting in January. The yearly RKKP report should include enough information to monitor adherence to the guidelines, new indicators and audit mechanisms can be added later if needed.

7. Appendix

Appendix 1 – Search strategy

"Sarcoma/radiotherapy"[Majr] AND "soft tissue sarcoma"[All Fields] AND ("humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])

(antal hits = 250)

Appendix 2 – Links to international radiotherapy soft tissue sarcoma guidelines

- Australian clinical practice guidelines for the management of adult onset sarcoma. Available at: https://wiki.cancer.org.au/australia/Clinical_question:What_is_the_evidence_for_radiotherapy_in_limb_and_extremity_soft_tissue_sarcoma_in_terms_of_local_recurrence,_survival_and_limb_salvage%3F. Accessed 2013.
- Scandinavian Sarcoma Group recommendation for radiotherapy of bone and soft tissue sarcoma: Available at: http://www.ssg-org.net/wp-content/uploads/2011/05/SSG-RT-Guidelines-December-2015.pdf. Accessed 2015.
- National comprehensive cancer network (NCCN) Clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf. Accessed 2018.

Appendix 3 – Radiotherapy guidelines in EpSSG soft tissue sarcoma protocols

1- EpSSG Rhabdomyosarcoma protocol

23. RADIOTHERAPY GUIDELINES

23.1 ROLE OF RADIOTHERAPY

Radiotherapy is an essential treatment for selected patients with rhabdomyosarcoma. This chapter gives guidelines about indications for radiotherapy, doses and target volume definitions. Here are some of the underlying data and the rationale for the recommendations shown.

IRS group I *(initial complete resection, no microscopic or macroscopic residual tumour, no lymph node involvement):*

Data from the IRS trials I, II and III have been published about the use of radiotherapy in patients with IRS group I tumours [1]. In the IRS-I trial, the use of radiotherapy was randomised, in IRS-II, no radiotherapy was recommended and in IRS-III, radiotherapy was indicated for patients with alveolar histology only. In the analysis of all 3 trials, there was a trend for increased failure free survival (not statistically significant) for patients with favourable histology who received radiotherapy, but the overall survival with or without radiotherapy was identical (about 95 % after 10 years). Failure free survival in the IRS trials I-III was significantly improved for patients with alveolar RMS who received radiotherapy. In IRS I and II, the overall survival for patients with alveolar RMS was also statistically significantly improved with radiotherapy (82 % vs. 52 % after 5 years). There was also a trend for improved overall survival in IRS-III (95 % vs. 86 %; p=0.23). The conclusion is that patients with alveolar RMS IRS group I benefit from radiotherapy, but not patients with favourable histology. This is also the policy in the current E*p*SSG radiotherapy guidelines.

IRS group II *(grossly resected tumour with microscopic residual disease or evidence of regional lymph node involvement):*

An analysis of radiotherapy in patients with IRS group II RMS and RMS-like tumours has been performed for patients treated in the CWS trials 81, 86, 91 and 96 [2]. Indications for radiotherapy differed amongst the trials, but there were favourable subgroups of patients that did not receive radiotherapy. Radiation doses ranged between 32 Gy and 54 Gy. There was a statistically significant difference in local control and event free survival in favour of patients treated with radiotherapy despite selection bias. Local control after 5 years was 83 % with and 65 % without radiotherapy ($p<0.004$), event free survival was 76 % with and 58 % without radiotherapy ($p<0.005$). There was a trend for improved survival in the radiation group (84 % vs. 77 %, n.s.). The improvement in local control and event free survival was independent of histology (favourable vs. unfavourable), tumour size, tumour site and age of the patient. Even patients with favourable histology and small primary tumours (< 5 cm) benefited from the use of radiotherapy. When the patients of each single trial (CWS 81, 86, 91 or 96) were analyzed separately, the difference in local control and event free survival was not statistically significant any more. The difference in overall survival for the whole study population, although better in all analyzed subgroups who received radiotherapy, was statistically significant only for patients with unfavourable histology (80 % vs. 56 % after 10 years).

In order to avoid a high local failure rate, the use of radiotherapy in patients with IRS group II is therefore recommended. This is compulsory for the patients treated in the high risk group. Because there is no statistically significant difference in overall survival for standard risk patients with

favourable histology, radiotherapy can be omitted if considering the tumour site and age of the patient, radiotherapy is too toxic. The risk of a higher local relapse rate must then be discussed.

IRS group III *(initial incomplete resection with gross residual disease):*

Radiotherapy is the only available local therapy in patients who cannot receive a secondary complete resection. Patients with vaginal tumours and favourable histology are usually very young and local control is acceptable without radiotherapy in patients in complete remission after chemotherapy [3, 4]. In patients with IRS group III disease at other sites with clinical complete remission without the option of second surgery and favourable histology, radiation doses of 32 Gy using accelerated hyperfractionation have resulted in satisfactory local control in the CWS trials [5,6]; with conventional fractionation, doses of 40 Gy or more have been reported to be sufficient to obtain local control [7]. For patients with alveolar RMS, a higher radiation dose has usually been given.

In the IRS IV trial, radiotherapy doses of 50.4 Gy in conventional fractionation were randomised against 59.4 Gy using hyperfractionation in patients with group III tumours [8]. The results with higher radiation doses were not improved, therefore 50 Gy is considered as sufficient for alveolar RMS independent of remission status and for embryonal RMS with residual disease following induction chemotherapy without an option for second surgery.

If delayed second surgery is possible and complete resection is achieved, patients still benefit from additional radiotherapy. In an analysis of the trials CWS 81, 86, 91 and 96, patients with RMS and RMS-like tumours who had IRS group III tumours with secondary complete resection (n=132) were evaluated. Indications for radiotherapy differed amongst the trials but radiotherapy was usually omitted in low risk patients. The calculated local control was 85 % for patients who did and 67 % for those who did not receive radiotherapy ($p<0.01$). EFS after 5 years was 77 % with and 58 % without radiotherapy ($p<0.02$). OS after 5 years with and without radiotherapy was 84 % and 79 % (n.s.). There was no difference in the incidence of systemic failures between the two groups. Patients with small as well as with large initial tumours profited from radiotherapy. The advantage for irradiated patients was seen in patients with favourable and unfavourable histology. The 5 year local control rate in patients without tumour cells in the resected specimen and no radiotherapy was 50 % compared with 89 % in those who did receive radiotherapy ($p<0.01$). Concerning patients with favourable histology and favourable site, overall survival is good following complete secondary resection even when postoperative radiotherapy is omitted, particularly in uro-genital non-bladder-prostate tumors. [3,4] Radiotherapy following second surgery is therefore usually indicated in this trial except for patients with favourable site and favourable histology (subgroup C). Moderate radiation doses are recommended (36 Gy or 41.4 Gy depending on histology). This is compulsary for the patients treated in the high risk group. Because there is no statistically significant difference in overall survival for standard risk patients with favorable histology, radiotherapy can be omitted if considering the tumour site and age of the patient, radiotherapy is too toxic. The risk of a higher local relapse rate must then be discussed.

23.2 EQUIPMENT

23.2.1 Megavoltage equipment

All patients will be treated with megavoltage equipment (4-20 MV linear accelerator preferably). For extremity tumours photons of 4 to 6 MV are recommended. Care must be taken to ensure an adequate skin dose in high risk areas when high energy photons are used. For tumours of the trunk, photons of 6 to 20 MV energy are recommended.

23.2.2 Electrons

Electrons are allowed for superficial and moderately infiltrating tumours (to a maximum depth of 5 cm) either as an electron field matching on, or as boost to, linear accelerator planned fields. The use

of electron fields alone should be avoided because of the late effects.

23.2.3 Brachytherapy

Brachytherapy may be used in cases of incompletely resected tumours of vagina, perineum, bladder, prostate and orbit. It may be used as boost technique before or after external beam irradiation or may in some cases replace external beam irradiation. This must be discussed with the reference centre for each individual patient. The dose for brachytherapy and external beam radiotherapy must take into account radiation-tolerance of adjacent tissue and should be calculated individually in each case.

23.3 TREATMENT PLANNING

3-D-conformal radiotherapy planning is recommended when critical structures lie in or nearby the target volume. The dose is prescribed according to ICRU 50.

23.4 RADIATION DOSE FOR THE PRIMARY TUMOUR

The radiation dose is prescribed according to histology of the tumour, response and the IRS group (extent of initial resection). The doses are summarized in table 1. This section relates to children aged 3 years and older.

- IRS group I (initial complete resection, no microscopic or macroscopic residual tumour, no lymph node involvement):

Radiotherapy is only performed in patients with alveolar RMS. The dose is 41.4 Gy in 23 fractions.
Exceptions: see below

- IRS group IIa (grossly resected tumour with microscopic residual disease, no evidence of regional lymph node involvement), IIb and c (with regional lymph node involvement):

All patients receive radiotherapy independently of histology. The dose is 41.4 Gy in 23 fractions.

- IRS group III (initial incomplete resection with gross residual disease):

In all patients with gross residual disease and residual disease following initial chemotherapy, a secondary complete resection is recommended. Second surgery should only be anticipated when a macroscopically and microscopically complete resection is possible. In case of second surgery, radiotherapy is usually given following second surgery. In patients with reconstructive second surgery, radiotherapy before this procedure may be recommendable.

Favourable (embryonal) histology:
Patients in subgroup C with complete secondary resection may not receive postoperative radiotherapy (see option A).
In all other patients, a dose of 36 Gy in 20 fractions is given following complete secondary resection and good clinical response at restaging following initial chemotherapy.
A dose of 41.4 Gy in 23 fractions is given following complete secondary resection and poor clinical response at restaging following initial chemotherapy.
In patients who receive radiotherapy *before* (expected) complete second surgery, the same doses according to response are applied.
The dose is 41.4 Gy in 23 fractions when there is complete clinical remission following initial chemotherapy and no second surgery is performed.
A dose of 50.4 Gy in 28 fractions is given following incomplete second surgery.
A dose of 50.4 Gy in 28 fractions is given in patients with residual tumour following initial chemotherapy (partial remission, progressive disease) when no second surgery is performed.
A boost of 5.4 Gy in 3 fractions may be given in large tumours with poor response to chemotherapy.

Unfavourable (alveolar) histology:
A dose of 41.4 Gy in 23 fractions is given following complete secondary resection.
In patients who receive radiotherapy *before* (expected) complete second surgery, the same dose is applied.
A dose of 50.4 Gy in 28 fractions is given following incomplete second surgery.
The dose is 50.4 Gy in 28 fractions when there is complete clinical remission following initial chemotherapy (no second surgery) and in patients with residual tumour following initial chemotherapy (partial remission, progressive disease) when no second surgery is performed. A boost of 5.4 Gy in 3 fractions may be given in large tumours with poor response to chemotherapy.
Radiotherapy of lymph nodes: see following chapter.
Exceptions: a. *Vaginal tumour* site and embryonal histology: no radiotherapy is performed if a complete remission is achieved after the completion of chemotherapy. In patients without complete remission, brachytherapy can be considered.
b. *Orbital tumour* site: The decision for or against radiotherapy in patients with group II and group III embryonal RMS is made individually following full informed consent. (see chapter treatment guidelines for special sites:orbit).
Patients with partial remission (more than 66 % tumor shrinkage) receive 45 Gy instead of 50.4 Gy.
c. *Patients < 3 years* of age: see paragraph 23.12.
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Important comment: The radiotherapy guidelines have to be followed strictly in all high risk patients. Furthermore they should be followed for patients treated in the standard risk group. As stated in the introduction of the radiotherapy chapter, event free survival is improved in patients with the use of radiotherapy in IRS groups II and III even when they had complete second surgery or are in complete clinical remission after initial chemotherapy. For patients in this situation presenting with favourable histology, despite differences in event free survival, there is no statistical difference in overall survival because of effective (but also aggressive) salvage treatment. Therefore, because of concerns of radiation-associated side effects, particularly in very young patients and/or vulnerable tumour sites, omission of radiotherapy may be justified in single patients who present with favourable histology and achieve clinical complete remission with chemotherapy and second surgery despite the higher risk of relapse. *This situation must be discussed with the reference centre and the patient/parents must be informed about the increased risk of local relapse.*

Table 7: **Radiation doses for the primary tumour according to histology and IRS - group for children age 3 years or older (RT: radiotherapy; F: fractions).**

IRS Group	**embryonal RMS**	**alveolar RMS**
I	no RT	41.4 Gy; 23 F
IIa, b and c	41.4 Gy; 23 F	41.4 Gy; 23 F
III followed by:		
- secondary complete resection	36 Gy; 20 F *(partial response)* 41.4 Gy; 23 *F (minor partial response, SD)* *Subgroup C: option A (no RT) or B (36 Gy)*	41.4 Gy; 23 F
- second look surgery but incomplete secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F
- clinical complete remission, no second look surgery	41.4 Gy; 23 F	50.4 Gy; 28 F
- partial remission, minor PR, SD, progressive disease, no second surgery	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F) orbit and PR (>2/3) 45 Gy; 25 F	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)

23.4.1 Radiation in patients with stable or progressive disease at restaging

Patients who have stable or progressive disease at restaging at week 9 receive second line therapy. Patients in whom a secondary complete resection is possible will be treated with postoperative radiotherapy with 41.4 Gy, 23 F independently of histology. Patients with inoperable tumours or with incomplete second surgery will be treated with 50.4 Gy in 28 fractions and a boost of 5.4 Gy in 3 fractions at the discretion of the treating radiation oncologist.

23.5 RADIATION DOSE FOR INVOLVED REGIONAL LYMPH NODES

Radiotherapy to regional lymph nodes is only performed when there is clinical or pathological evidence of lymph node involvement. Radiotherapy is not performed when there is no evidence of lymph node involvement at diagnosis, either clinically or histologically. The risk of lymph node involvement in patients with embryonal RMS is very low, it is higher in patients with alveolar RMS. In the CWS trials 81-96, there were 184 patients with alveolar RMS without clinically involved lymph nodes at diagnosis. The incidence of loco-regional lymph node failure was 9 % overall. Analyzed according to tumour site, it was highest for extremity tumours (14 %;11 of 78 pts.). There was no difference in the incidence according to IRS group or according to age. Of the 17 lymph node relapses, only 7 were isolated relapses. Radiotherapy of clinically uninvolved regional lymph nodes seems therefore not justified.
Radiotherapy to the involved lymph node sites is performed independently of histology. In patients

with clinical or pathological evidence of lymph node involvement, a radiation dose of 41.4 Gy is given when there are no enlarged lymph nodes following initial chemotherapy before the onset of radiotherapy. This dose is given also when a lymph node excision was performed initially. In patients with enlarged lymph nodes at the onset of radiotherapy, an additional boost of 9 Gy is applied.

Table 8: **Radiation dose for regional lymph node areas (RT: radiotherapy; F:fractions)**

Situation	**embryonal/alveolar RMS**
no clinical or pathological involvement of regional lymph nodes	no RT
clinically or pathologically positive lymph nodes; excised or in complete remission before RT	41.4 Gy; 23 F
positive lymph nodes, macroscopical residual disease before RT	41.4 Gy; 23 F + 9 Gy boost; 5 F

23.6 FRACTIONATION

Treatment is applied in conventional fractionation with 1.8 Gy per day. In patients with large abdominal or cranio-spinal fields, smaller fractions are used. In patients < 3 years of age, smaller fractions may be used as well (1.6 Gy). The radiation dose is prescribed according to ICRU 50.

23.7 COMPENSATION FOR TREATMENT BREAKS

Standard fractionation is 5 days per week. If there is a treatment interruption, 2 fractions with an interval of at least 6 hours between fractions should be given to enable completion of treatment within the same overall time if feasible from the irradiated volume.

23.8 TARGET VOLUME DEFINITION FOR PRIMARY TUMOUR

1. The target volume is chosen according to the initial tumour volume (gross tumour volume; GTV). The pretherapeutic T1 MR image with contrast is usually the optimal imaging study. Exceptions: intrathoracic or pelvic tumour bulk (see paragraph 23.14)
2. The clinical target volume (CTV) is defined as the GTV + 1 cm (exception limbs: 2 cm in longitudinal direction).
3. Additionally, scars of the biopsy, of the initial surgery, of the second look surgery and of drain sites have to be included in the CTV. Furthermore all tissues that were potentially tumourcontaminated
during surgery need to be included in the CTV.
4. The planning target volume (PTV) is defined as the CTV + 1 cm (exception chest wall: 2 cm). orbit: whole orbit included in the PTV up to 36 Gy).
5. In patients receiving 50.4 Gy, the CTV and hence the PTV is reduced by 1 cm after 41.4 Gy.

In patients with orbital tumors, the initial radiation of the whole orbit is reduced to the initial tumor extent + 1 cm after 36 Gy.
6. In patients receiving a boost after 50.4 Gy, the PTV for the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.
7. In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields. The same should be observed for vertebral bodies in order to avoid scoliosis.
Summary: The PTV consists of the initial tumour volume + 2 cm except for limb and chest wall tumours (+ 3 cm) for 41.4 Gy and except for orbit (entire orbit for 36 Gy). Areas contaminated during surgery including scars and drainage sites must be included in the PTV. If 50.4 Gy need to be applied, the PTV is reduced by 1 cm after 41.4 Gy (orbit: initial tumor size + 1 cm after 36 Gy).

23.9 TARGET VOLUME DEFINITION FOR LYMPH NODES

The dose of 41.4 Gy is applied to the entire lymph node site (axilla, groin, paraaortic lymph nodes etc.). When that approach results in very large radiation fields, this extent can be reduced to the involved lymph nodes plus a PTV margin of 3 cm at the discretion of the treating radiation oncologist. The boost is used for the enlarged lymph node(s) as it is defined in the CT or ultrasound examination before the onset of radiotherapy. An additional margin of 2 cm is to be used for the PTV of the boost.
If possible the draining lymphatic vessels between the primary tumour and the involved lymph node site should be irradiated. However, in some cases this would result in unacceptable large radiation fields. In these patients, two separate radiation fields have to be used to treat the primary tumour and the lymph node site excluding draining lymphatic vessels.

23.10 TIMING OF RADIOTHERAPY

In patients with IRS group III (macroscopical residual disease), the option for second surgery must be checked before the onset of radiotherapy. In patients receiving no second surgery, radiotherapy is performed at week 13. In high risk patients, the full dose of doxorubicin must have been given before the onset of radiotherapy.
After second surgery, postoperative radiotherapy should be started within 21 days except when there are postoperative complications.
In patients who receive reconstructive surgery, radiotherapy before second look surgery may be beneficial. This must be discussed with the study centre. The interval between the end of radiotherapy and second surgery should be approximately 5 weeks. Surgery immediately following radiotherapy can result in higher operative morbidity.

23.11 SYNCHRONOUS CHEMOTHERAPY AND RADIOTHERAPY

Synchronous application of radiotherapy and chemotherapy with doxorubicin and actinomycin D should in general be avoided.
However irradiation will take from 5 to 6 weeks and it is important not to reduce excessively the cumulative dose of the drugs administered.
According to the protocol the whole dose of doxorubicin will be administered before start of radiotherapy.
Parallel application of radiotherapy and actinomycin D should be given:
- when extremity tumours are treated
- mucosae are not included in the irradiation field.
- at the very beginning of RT (week 13)

Actinomycin-D should be omitted at week 16 when the treatment fields include the trunk, abdomen, or the head and neck
Caution is needed in the administration of Actinomycin-D at week 19: in general if 2 weeks have passed from the end of irradiation Actinomycin-D should be given. In case of a shorter interval Actinomycin-D may be re administered when no toxicity is anticipated (in case of doubt reduce Actinomycin dose to 50%)
The omitted doses of actinomycin will not be administered later.

23.12 AGE ADAPTATION

23.12.1 Age > 1 and < 3 years at the time of radiotherapy

Embryonal RMS: Radiotherapy will only be performed if there is residual disease at the end of chemotherapy.
Exception: parameningeal tumours will always receive radiotherapy even when in complete clinical remission after chemotherapy. The radiation dose should be given according to older patients. Depending on tumour size and site, this can result in unacceptable toxicity. In these special cases, a dose reduction can be performed. This should be discussed with the reference center.
Alveolar RMS: Group I: no radiotherapy
Group II and III: radiotherapy according to older patients (no dose reduction; exceptions as above)
Smaller fraction sizes can be used (1.5 or 1.6 Gy).

23.12.2 Age < 1 year

An individual decision for or against radiotherapy must be made depending on tumour histology, tumour site, response to chemotherapy, extent of previous resections and options for second surgery. This should be discussed with the study centre.

23.13 NORMAL TISSUE TOLERANCE GUIDELINES

	Conventional fractionation (F:fraction)
heart	**30.6** Gy; 17 F
whole liver	**19.8** Gy; 11 F
whole kidney	**14.4** Gy; 8 F
spinal cord (part) spinal cord in pts. with residual spinal tumour (on MRI)	**41.4** Gy; 23 F **50** Gy; 28 F
optic nerve/optic chiasm	**45** Gy; 25 F

23.14 TREATMENT GUIDELINES FOR SPECIAL SITES

23.14.1 Parameningeal tumours

Surgery in parameningeal tumours is usually incomplete. Therefore second surgery should not be

performed. Radiotherapy must be applied at week 13.

23.14.2 No skull base erosion/no cranial nerve palsy

The brain/meninges are NOT routinely irradiated. The CNS volume irradiated will be that included within the fields required to cover the primary volume, (e.g. nasopharynx/paraspinal situations) according to the general guidelines.

23.14.3 Skull base erosion/cranial nerve palsy/no intracerebral component

RMS with skull base erosion/cranial nerve palsy but no intracerebral components will be irradiated as follows:
The PTV will be that required to treat the primary tumour (initial tumour volume + 2 cm).
Radiation fields must adequately cover the initial skull base erosion but there is no routine whole brain irradiation.

23.14.4 Skull base erosion/cranial nerve palsy/with intracranial component

The PTV for the intracranial extent of the tumour is defined according to the residual intracranial component at restaging before the onset of radiotherapy with an additional safety margin of 2 cm. It is not necessary to consider the full initial intracranial tumour extent. The amount of skull base included in the PTV is as defined above.

23.14.5 Disseminated meningeal disease or CSF positive cytology

These patients are treated in the protocol for metastatic disease.

23.14.6 Target volume definition in parameningeal RMS with positive lymph nodes

The PTV is according to the treatment guidelines for parameningeal site and to the treatment guidelines for nodal involvement.

23.14.7 Head and neck non-parameningeal

Radiotherapy is given according to the general radiation guidelines described above. Patients in subgroup C (favourable histology) may not receive radiotherapy when a secondary complete resection was performed.

23.14.8 Orbit

The decision for or against radiotherapy in patients with group II and group III embryonal RMS and clinical complete remission following induction chemotherapy is made individually following full informed consent. Patients in this treatment situation who receive radiotherapy have a lower risk of local relapse, an improved event free survival but experience radiation associated side effects. Patients in this treatment situation who do not receive radiotherapy have a higher risk of local relapse, less good event free survival but no radiation associated side effects in case there is no local relapse and increased toxicity due to salvage treatment including radiotherapy if a relapse occurs. Overall survival in both approaches is equivalent. This is due to effective salvage treatment[9]. The decision for or against radiotherapy is therefore a question of priorities of the treating physician and of the patient/parents. Two options are given in this protocol (see chapter 14.4)
When given, radiation of the entire orbit is performed up to 36 Gy, then the PTV is reduced to the initial tumor size and an additional margin of 1 cm, if possible sparing the lacrimal gland. Patients with favourable histology and clinical complete remission following induction chemotherapy receive 41.4 Gy, patients with partial response (>2/3) 45 Gy, patients with minor partial response, SD or PD receive 50.4 Gy.

23.14.9 Extremities

Extremity tumours should be treated according to the general guidelines described above. Tissue contaminated during surgery must be included in the CTV. After surgical procedures, all scars and drainage sites should be irradiated with a safety margin of 1 - 2 cm. Circumferential radiotherapy must be avoided because of the danger of constrictive fibrosis and lymphoedema. In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from

the tumour extension, be excluded from the radiation fields.
For lymph node positive extremity RMS see paragraphs 2.4 and 2.8.

23.14.10 Urogenital Bladder/Prostate Site

The doses and target volume definitions follow the general guidelines. Gonads should be positioned out of the treatment volume if possible (in girls oophoropexy must be discussed). Depending on the extent and infiltration of the disease, patients with bladder/prostate tumours may be treated with afterloading techniques/brachytherapy. Individual planning and discussion with the respective reference centre is advised.

23.14.11 Urogenital Non-Bladder/Prostate Site

Patients in subgroup C (favourable histology) with complete secondary resection may not receive postoperative radiotherapy (see chapter 14.4)
Incompletely resected paratesticular RMS need to be irradiated. In order to avoid late sequelae all non mutilating surgical possibilities should be exhausted. In case radiotherapy is necessary (microscopically complete resection not possible), the dose according to the general guidelines should be given with a PTV margin of 2 cm around the initial tumour volume. The contralateral testicle should be positioned out of the treatment volume if possible (orchidopexy). Radiotherapy to lymph node sites is performed according to the general recommendations. When there is scrotal involvement, the infiltrated scrotal area must be treated with a PTV margin of 2 cm.
RMS of the vagina with favourable histology (embryonal RMS) do not receive radiotherapy if in clinical complete remission after chemotherapy. Patients with unfavourable histology (alveolar RMS) and patients who are not in complete clinical remission after chemotherapy need to be treated with radiotherapy. Depending on the extent and infiltration of the disease these patients may be treated with afterloading techniques/brachytherapy. Individual planning and discussion with the respective reference centre is advised. Oophoropexy has to be considered in order to avoid radiation doses at the ovary in all girls treated for pelvic tumours.

23.14.12 Abdomen

Intraperitoneal RMS or RMS of small and large bowel should be resected and only rarely irradiated. Abdominal structures most often prevent high radiation doses.
If radiotherapy to the abdomen is performed, the kidney and liver tolerance doses have to be respected (see paragraph 2.12). In growing patients, a radiation dose gradient through vertebral bodies should be avoided because of the risk of scoliosis. Vertebral bodies and pedicles should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields.
Whole abdominal radiotherapy is performed only when there is malignant ascites or gross tumour spillage during surgery. These patients will be treated in the protocol for metastatic RMS.

23.14.13 Pelvis

Small bowel/iliocoecal bowel may be displaced from the pelvis by treating the patient in prone position and by using a belly board. In some cases, bowel can be spared with special surgical techniques using a tissue expander.
Tumours with non-infiltrating extension into the preformed pelvic cavity often show a large intrapelvic mass which shrinks dramatically after chemotherapy. Irradiating the pre-treatment volume would mean that large volumes of normal tissue (bowel and bladder) are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after chemotherapy at the beginning of radiotherapy and a 2 cm safety margin. For all other parts of the tumour (infiltrated muscle or bone), the general safety margins according to the initial tumour extension are to be applied.

23.14.14 Retroperitoneum

RMS of the retroperitoneum should be irradiated as outlined in the general radiotherapy guidelines and treatment planning should be CT-based. Tolerance doses of organs in this region need to be

respected (i.e. kidneys, bowel, spinal cord). Dose volume histograms for these organs are strongly recommended. In order to avoid scoliosis in growing patients the vertebral bodies should either be irradiated symmetrically or shielded.

23.14.15 Chest wall

The doses and target volume definitions follow the general guidelines.
Tumours with non-infiltrating extension into the preformed thoracic cavity often show a large intrathoracic mass which shrinks dramatically after chemotherapy. Irradiating the pre-treatment volume would mean that large volumes of lung tissue are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after chemotherapy at the beginning of radiotherapy and a 2 cm safety margin. For all other parts of the tumour (infiltrated muscle or bone), the general safety margins according to the initial tumour extension are to be applied.
Radiotherapy of the hemithorax is performed only when there is malignant pleural effusion or gross tumour spillage during surgery. These patients will be treated in the protocol for metastatic RMS.

23.15 QUALITY ASSURANCE OF RADIOTHERAPY

Radiotherapy documentation forms will be completed and submitted via the relevant data office for review by the Radiotherapy Committee. Simulator films, plans and diagnostic films which determined treatment volume will be requested in all cases who fail locally after radiotherapy and in randomly selected cases of those who do not fail as part of a quality assurance assessment. This will be co-ordinated by the Radiotherapy Committee who will contact centres for films from individual patients as requested.

23.16 REFERENCES – RADIOTHERAPY

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Appendix 3 – Radiotherapy guidelines in EpSSG soft tissue sarcoma protocols

2- EpSSG non-rhabdomyosarcoma protocol

14 Radiotherapy guidelines

Radiotherapy is an essential component of the treatment strategy for NRSTS.
The use of radiotherapy is a balance between the prognostic improvement due to radiotherapy and the potential side effects of the treatment. In adults, radiotherapy is required in most patients after wide excision, especially in large tumours, and irradiation is considered always unnecessary only after compartment resection. The situation in children and adolescents is different: the morbidity of radiotherapy is clearly much greater than in adults (depending on the site that require irradiation) since these patients are growing and physical development can be disturbed.
In adult studies, relatively high total dose of conventional fractionated external beam irradiation are recommended to achieve local control: doses of 60-64 Gy are used, sometimes with 50 Gy on a large first volume and a boost on a smaller one. Radiotherapy is usually delivered following surgery (post-operative radiotherapy), but excellent results have been reported with pre-operative irradiation. For children and adolescents, so far lower radiation doses of about 50 Gy have been used in the CWS-trials.
The rationale, indications and doses of radiotherapy in synovial sarcoma and adult type NRSTS are given below.

14.1 Equipment

► Megavoltage equipment

All patients will be treated with megavoltage equipment (4-20 MV linear accelerator preferably). For extremity tumours photons of 4 to 6 MV are recommended. Care must be taken to ensure an adequate skin dose in high risk areas when high energy photons are used. For tumours of the trunk, photons of 6 to 20 MV energy are recommended.

► Electrons

Electrons are allowed for superficial and moderately infiltrating tumours (to a maximum depth of 5 cm) either as an electron field matching on, or as boost to, linear accelerator planned fields. The use of electron fields alone should be avoided because of the late effects.

► Brachytherapy

Brachytherapy may be used in cases of incompletely resected tumours of vagina, perineum, bladder, prostate and orbit. It may be used as boost technique before or after external beam irradiation or may in some cases replace external beam irradiation. This must be discussed with the reference centre for each individual patient. The dose for brachytherapy and external beam radiotherapy must take into account radiation-tolerance of adjacent tissue and should be calculated individually in each case.

14.2 Treatment planning

3-D-conformal radiotherapy planning is recommended when critical structures lie in or nearby the target volume. The dose is prescribed according to ICRU 50.

14.3 Fractionation

Treatment is applied in **conventional fractionation with 1.8 Gy per day, 5 day per week**. In patients with large fields, smaller fractions may be used. In patients < 3 years of age, smaller fractions may be given as well (1.6 Gy). The radiation dose is prescribed according to ICRU 50.

►►► Compensation for treatment breaks

Standard fractionation is 5 days per week. If there is a treatment interruption, 2 fractions with an interval of at least 6 hours between fractions should be given to enable completion of treatment within the same overall time, if fesible from the surrounding critical structures.

14.4 Target volume definition for primary tumour

 The target volume is chosen according to the initial tumour volume (gross tumour volume - GTV). The pre-therapeutic T1 MRI image with contrast is usually the optimal imaging study.

_ Exceptions: intrathoracic or pelvic tumour bulk

 The clinical target volume (CTV) is defined as the GTV + 1 cm

_ Exception limbs: 2 cm in longitudinal direction

 Additionally, scars of the biopsy, of the initial surgery, of the second look surgery and of drain sites have to be included in the CTV. Furthermore all tissues that were potentially tumour-contaminated during surgery need to be included in the CTV.

 The planning target volume (PTV) is defined as the CTV + 1 cm

_ Exception chest wall: 2 cm

 In patients receiving a boost after 50.4 Gy, the PTV of the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.

 In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields. The same should be observed for vertebral bodies in order to avoid scoliosis.

***Summary**:*

The PTV consists of the initial tumour volume + 2 cm except for limb and chest wall tumours (+ 3 cm). Areas contaminated during surgery including scars and drainage sites must be included in the PTV. If more than 50.4 Gy need to be applied, the PTV of the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.

14.5 Target volume definition for lymph nodes

In case of involved lymph nodes:

1. Radiotherapy could be avoided in case of radical lymphadenectomy (surgical removal of all the lymph nodes of the involved site).

2. After biopsy or non-radical resection (surgical removal of the involved nodes but not of all the lymph nodes of the involved site) radiotherapy is required. The dose of **50.4 Gy** is applied to the entire lymph node site (axilla, groin, paraaortic lymph nodes etc.). When that approach results in very large radiation fields, this extent can be reduced to the involved lymph nodes plus a PTV margin of 3 cm at the discretion of the treating radiation oncologist.

3. In case of still enlarged lymph nodes at the time of radiotherapy, lymph nodes receive an additional boost up to a total dose of **59.4 Gy** if feasible from the surrounding critical structures (PTV definition for the boost as for the boost of primary tumour).

If possible the draining lymphatic vessels between the primary tumour and the involved lymph node site should be irradiated. However, in some cases this would result in unacceptable large radiation fields. In these patients, two separate radiation fields have to be used to treat the primary tumour and the lymph node site excluding draining lymphatic vessels.

14.6 Timing of radiotherapy

Since the value of chemotherapy is not clear, radiotherapy should not be delayed when radiotherapy and chemotherapy are given.

In patients submitted to initial gross resection, radiotherapy should start at least after 3 cycles of

chemotherapy. Radiotherapy plans should be performed during the 7° week, with the aim to start the irradiation at **week 9**, at the resolution of the toxicity of the third cycle of chemotherapy.
During the administration of radiotherapy (5-6 weeks, overlapping with 2 chemotherapy cycles) chemotherapy will be given with ifosfamide alone.
In patients with IRS group III (macroscopical residual disease), the option for second surgery must be checked before the onset of radiotherapy.
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:
- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy

When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy (and after the last chemotherapy cycle) to avoid surgical complications.
When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.

14.7 Indications and doses

► Synovial sarcoma:
IRS group I _ no RXT
IRS group II δ **5 cm _** 50.4 Gy (1.8 Gy/d)
> 5 cm _ 54 Gy (1.8 Gy/d)
* RXT could be avoided in selected cases (i.e. age < 10 years)
IRS III
different options in relation to delayed surgery
(and to age and initial tumour size)
_ no RXT
_ pre-op RXT 50.4 Gy
_ post-op RXT 50.4 Gy (“R0”)
_ post-op RXT 54 Gy (“R1”)
_ definitive RXT 59.4 Gy

► Adult type NRSTS:
IRS group I δ **5 cm _** no RXT
> 5 cm G1 _ no RXT
G2 _ RXT 50.4 Gy
G3 _ RXT 50.4 Gy
IRS group II G1 _ no RXT
G2 _ 54 Gy
G3 _ 54 Gy
IRS III
different options in relation to delayed surgery
(and to age and initial tumour size)
_ no RXT
_ pre-op RXT 50.4 Gy
_ post-op RXT 50.4 Gy (“R0”)
_ post-op RXT 54 Gy (“R1”)
_ definitive RXT 59.4 Gy

14.8 Normal tissue tolerance guidelines

Conventional fractionation
(F:fraction)
Heart **30.6** Gy; 17 F
whole liver **19.8** Gy; 11 F
whole kidney **14.4** Gy; 8 F
spinal cord (part)
spinal cord in pts. with residual paraspinal tumour (on MRI)
41.4 Gy; 23 F
50 Gy; 28 F
optic nerve/optic chiasm **45** Gy; 25 F

14.9 Treatment guidelines for special sites

Parameningeal tumours
In case of skull base erosion and cranial nerve palsy, the PTV will be that required to treat the primary tumour (initial tumour volume + 2 cm). Radiation fields must adequately cover the initial skull base erosion but there is no routine whole brain irradiation.

Extremities
Extremity tumours should be treated according to the general guidelines described above. Tissue contaminated during surgery must be included in the CTV. After surgical procedures, all scars and drainage sites should be irradiated with a safety margin of 1 - 2 cm. Circumferential radiotherapy must be avoided because of the danger of constrictive fibrosis and lymphedema. In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields.

Urogenital Site
The doses and target volume definitions follow the general guidelines. Gonads should be positioned out of the treatment volume if possible (in girls oophoropexy must be discussed!). Individual planning and discussion with the respective reference centre is advised.

Abdomen
The kidney and liver tolerance doses have to be respected. In growing patients, a radiation dose gradient through vertebral bodies should be avoided because of the risk of scoliosis. Vertebral bodies and pedicles should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields.

Pelvis
Small bowel/iliocoecal bowel may be displaced from the pelvis by treating the patient in prone position and by using a belly board. In some cases, bowel can be spared with special surgical techniques using a spacer. Tumours with non-infiltrating extension into the preformed pelvic cavity often show a large intrapelvic mass. Irradiating the pre-treatment volume would mean that large volumes of normal tissue (bowel and bladder) are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after surgery/chemotherapy at the beginning of radiotherapy and a 2 cm safety margin. For all other parts of the tumour (infiltrated muscle, bone or organs), the general safety margins according to the initial tumour extension are to be applied.

Retroperitoneum
Tolerance doses of organs in this region need to be respected (i.e. kidneys, bowel, spinal cord). Dose volume histograms for these organs are strongly recommended. In order to avoid scoliosis in growing patients the vertebral bodies should either be irradiated symmetrically or shielded.

Chest wall

The doses and target volume definitions follow the general guidelines. Tumours with noninfiltrating extension into the preformed thoracic cavity often show a large intrathoracic mass.
Irradiating the pre-treatment volume would mean that large volumes of lung tissue are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after surgery/chemotherapy at the beginning of radiotherapy and a 3 cm safety margin. For all other parts of the tumour (infiltrated muscle or bone), the general safety margins according to the initial tumour extension are to be applied.

14.10 Quality assurance of radiotherapy

Radiotherapy documentation forms will be completed and submitted via the relevant data office for review by the Radiotherapy Committee. Simulator films, plans and diagnostic films which determined treatment volume will be requested in all cases who fail locally after radiotherapy and in randomly selected cases of those who do not fail as part of a quality assurance assessment. This will be co-ordinated by the Radiotherapy Committee who will contact centres for films from individual patients as requested.

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Synovial sarcoma

17.2 Radiotherapy

Concerning radiotherapy, as for other STS, it will be given as conventional fractionation of 1.8 Gy/day. The total dose will range between 50.4 and 59.4 Gy.

► IRS Group I (initial complete resection, R0):

The INT Milan series seemed to suggest a favourable trend for post-operative radiotherapy in patients previously submitted to complete resection (with no statistically significant difference).

post-operative radiotherapy
yes no
5 year LRFS complete resection (n.patients 144) 77.8% (n.51) 66.9% (n.93)
complete resection, tumour ≤ 5 cm (n.63) 100% (n.19) 75.9% (n.44)
complete resection, tumour > 5 cm (n.72) 73.1% (n.30) 60.9% (n.42)
5 year LRFS marginal resection (n.71) 57.4% (n.56) **7.1%** (n.15)
EpSSG NRSTS 2005 protocol
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In the common ICG-CWS analysis, no benefit of adding radiotherapy in IRS group I patients (complete macroscopic and microscopic resection) was observed, independent on the initial tumour size. So far there is no clear evidence of the role of radiotherapy in these patients. Since large initial tumour size is a recognized risk factor stopping rules for local failures for patients with tumours larger than 5 cm in diameter at diagnoses will be defined.

► IRS group II (microscopic residual disease at initial resection or positive lymph nodes):

Important note:
Every effort should be done by the surgeon to avoid IRS group II patients (the use of primary reexcision
is recommended, when feasible).

In the CWS-ICG-analysis, the treatment results for patients in IRS group II were comparable to those in IRS group I. These results were obtained with nearly all patients in IRS II receiving radiotherapy.

The multicenter analysis from the M.D. Anderson *(Okcu F, J Clin Oncol 2003)* showed the benefit of post-operative radiotherapy on LRFS and OS in group I-II patients.

In the analysis of the INT Milan data, a clear benefit was observed for group II patients who received radiotherapy: 5-year LRFS was 7% in the 15 group II patients treated without irradiation. This series regards patients of all ages, mainly adults *(Ferrari A, Cancer 2004).*

These findings would suggest the use of radiotherapy after marginal resection.

In the cohort of 66 paediatric patients with synovial sarcoma enrolled in the SIOP MMT 84-89-95 studies, 22 patients initially submitted to microscopically incomplete resection were seen. All of them received chemotherapy (IVA), while radiotherapy was given to 5 patients only (17 did not receive radiotherapy).

Local relapses were seen in 1/5 patients treated with radiotherapy (then the child was salvaged with second-line therapy).

Among the 17 patients treated without irradiation, 3 patients had local relapse and 2 had metastatic relapse: 1 out of the 3 local relapsing patients and 1 of the patients who developed metastases died of their disease; at the end, 20/22 IRS group II patients were alive in first (16) or second (4) remission at the time of the analysis.

Concerning radiotherapy, 12 patients with initial microscopically incomplete resection were cured without radiotherapy, and therefore without radiotherapy-related side effects.

These findings may suggest that radiotherapy could be avoided in some IRS group II patients, at least those with younger age and small tumour size.
The debate on indication for radiotherapy in IRS II patients has its background on the different philosophies adopted over the years by the CWS-ICG groups and the SIOP group. It is important to underline the concept of the "total burden of therapy" experienced by a given patient and the predicted sequelae that treatments may have. In particular, the philosophy behind the SIOP-MMT studies has pointed to a lesser use of radiotherapy in selected subsets of patients, i.e. children submitted to marginal resection at diagnosis, with suspected microscopical residual disease: this strategy generally produced worse local relapse rates than those reported elsewhere, but the overall survival was superimposable, since a significant number of locally relapsing patients were cured by salvage treatments (including aggressive surgery and radiotherapy); on the other hand, a significant proportion of patients could be cured without radiotherapy. In other words, according to this strategy, outcome should be measured on the combination of overall survival and "cost" of survival in terms of sequelae, rather than on disease-free survival alone.
EpSSG NRSTS 2005 protocol
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This is yet matter of debate.
The E*p*SSG NRSTS 2005 protocol will suggest the use of **radiotherapy in IRS group II** synovial sarcomas (as required by ICG-CWS groups), but an **alternative option** may be to avoid irradiation, in particular for younger patients (age less than 10 years) and tumour size smaller than 5 cm (SIOP option). The multidisciplinary discussion may determine the decision in individual case.
Radiotherapy will be applied in conventional fractionation. The total radiation dose for patients with tumours < 5 cm in diameter is **50.4 Gy** in 1.8 Gy fractions. Because of a higher local failure risk in patients with larger tumours, **54 Gy** are given in patients with > 5 cm initial tumour size.
In order to avoid concomitant administration of doxorubicin and radiotherapy (that will last 5-6 weeks, overlapping with 2 chemotherapy cycles), in group II ≤ 5 cm patients (3 cycles of chemotherapy required), radiotherapy will start after the completion of the 3 chemotherapy cycles, avoiding the need of concomitant chemo-radiotherapy.
In group II > 5 cm, radiotherapy cannot be delayed at the end of chemotherapy (18th week). Therefore, radiotherapy will start at 9th week and will be administered concomitantly to 4th and 5th cycles of chemotherapy (ifosfamide alone)

► IRS group III (macroscopic residual disease at initial resection):

After the initial 3 cycles of chemotherapy, tumour-reassessment and then local treatment need to be planned.
Four different options are possible:

a. Patients with the option of secondary complete resection:

Surgery remains the mainstay of treatment for synovial sarcomas.
The use of radiotherapy is a matter of debate in patients with secondary complete resection.
In the CWS group, nearly all patients treated with complete second surgery received radiotherapy.
In INT Milan series, 30 out of 40 IRS group III patients had delayed complete resection: 11 of them received radiotherapy, 19 did not, and no difference was observed on the outcome. Survival rates strongly correlated with the chances to achieving complete surgery (5-year EFS 42% vs 10%), though metastases (and not the local relapse) were the main cause of treatment failure (5-year LRFS 80%, MFS 34%) *(Ferrari A, Cancer 2004)*.
In the E*p*SSG centers, there is no a consensus on:
1) the necessity to give radiotherapy after delayed complete surgery; it is not clear whether the use of radiotherapy in these patients results in improved survival

2) what is the best option, when the decision to give radiotherapy has been taken, between preoperative
and post-operative radiotherapy
(pre-operative irradiation can improve the chance to perform a complete secondary resection; moreover, pre-operative radiotherapy could be more effective in non-hypoxic tissues, may reduce the risk of intra-operative contamination, and could use smaller radiotherapy fields; post-operative radiotherapy has a small risk of wound complication).
Therefore, there are three treatment options for patients with the option of secondary complete resection:
a1. Preoperative RXT with **50.4 Gy** in 1.8 Gy daily fractions
EpSSG NRSTS 2005 protocol
64
a2. No additional RXT following secondary complete resection
a3. Postoperative RXT with **50.4 Gy** in 1.8 Gy daily fraction
The decision may depend also to the physician's preference.
However, possible suggestions are:
- to avoid RXT in younger patients after delayed complete surgery (< 6 years)
- to give RXT in case of initial large tumour size (> 10 cm) and in case on first surgical approach (biopsy) that could have caused tissue contamination.
The results of the different local modality groups will be compared
a.4 Following secondary incomplete resection, **54 Gy** have to be given with microscopical residual disease. In case of macroscopic residual disease, radiotherapy has to be given according to patients with no second surgery (see below)
b. Patients without the option of secondary complete resection:
IRS group III patients who cannot have a complete secondary resection have a poor prognosis and need to have radiotherapy. Radiotherapy is then the only local therapy modality and should be given with high doses. The recommended dose is **59.4 Gy**.
An additional boost of 5.4 Gy can be given when there is residual disease at the end of radiotherapy.
The dose recommendation may need modification depending on the age of the patient and the tumour site.

Timing of radiotherapy
IRS group II:
Radiotherapy should start after 3 cycles of chemotherapy. Radiotherapy plans should be performed during the 7th week, with the aim to start the irradiation at **week 9**, at the resolution of the toxicity of the third cycle of chemotherapy.
During the administration of radiotherapy (5-6 weeks, overlapping with 2 chemotherapy cycles) chemotherapy will be given with ifosfamide alone (patients with tumour > 5 cm).
IRS group III:
The option for second surgery must be checked before the onset of radiotherapy.
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:
- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy
When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy (and after the last chemotherapy cycle) to avoid surgical complications.

When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.

►►► Radiotherapy in younger children

Children < 3 years of age

Radiotherapy is only given when there is residual tumour after primary or secondary resection. For patients in IRS group III without an option of secondary complete resection, the dose is reduced to 50.4 Gy

- IRS group I: no RXT
- IRS group II: no RXT
- IRS group III, secondary complete resection: no RT
- IRS group III, no secondary surgery: 50.4 Gy

Adult type STS

18.2 Radiotherapy

► IRS Group I (initial complete resection, R0):

In adult patients with soft tissue sarcoma, radiotherapy is required after incomplete resection, but often also after wide excision, especially in case of large tumour. In children with a higher risk of severe late effects of radiotherapy, the indication has to be stricter than in adults.

There is little data about the impact of radiotherapy in IRS group I patients in paediatric age. In the analysis of the St. Judes experience of patients with at least grossly resected tumours, univariate analysis of factors associated with improved local control included the use of radiotherapy. It is of note, though, that the majority of irradiated patients belonged to IRS group II. (*Spunt S, 2002*).

In the INT Milan series, 100 paediatric patients were classified as IRS group I: 22 received postoperative
radiotherapy and 78 did not. LRFS at 5 years was 95.2% in the group of patients who had radiotherapy and 84.4% in the second group, without statistically significant difference. When only patients with tumour larger than 5 cm were considered, 5-year LRFS and OS were 91.7% and 90.0% for patients treated with radiotherapy (13 cases) and 69.8% and 53.8%, respectively, for those who were not irradiated (23 cases), and the p value was significant for OS (though the OS results may be influenced by the different use of chemotherapy in this two groups, the percentage of patients who had also chemotherapy being higher in the first group) (*Ferrari A, J Clin Oncol 2005*).

However:

- because of the low risk of local failure in patients with small tumours, no radiotherapy is given in patients in IRS group I with < 5 cm tumour diameter at diagnosis.
- in IRS group I patients with tumours > 5 cm, radiotherapy is given in G2 and G3 tumours (no in G1 tumour). In case of local relapses, these patients are at risk of metastatic relapse and consequently impaired prognosis. The radiation dose of adjuvant radiotherapy is **50.4 Gy** in 1.8 Gy fractions.

► IRS group II (microscopic residual disease at initial resection):

Patients with microscopic residual disease following secondary complete resection are at a considerable risk to develop local recurrences. In the INT Milan series, 5-year LRFS was 75.7% in patients who had radiotherapy (n = 27) and 55.6% in those who did not receive it (n = 9) (*Ferrari A,J Clin Oncol 2005*)

An exception is low-grade tumours. The risk of relapse is lower, and furthermore local recurrences are usually again low-grade, are hardly ever associated with systemic failure, and could be treated with success with re-surgery and eventual radiotherapy. COG (Children's Oncology group) series included 4 IRS group II G1 patients treated without radiotherapy who did not relapse (*unpublished data*). In the INT Mila series, 3 patients were classified as group II/G1: two received radiotherapy, and one did not; this patient relapsed locally, but he was salvage with surgery and radiotherapy. Therefore, no radiotherapy is recommended in patients with IRS group II G1 tumours.

An exception is patients in whom surgery of local recurrence would be problematic because of tumour site or because of the extent of primary surgery. In these cases, radiotherapy should be given at primary treatment (54 Gy).

In patients IRS group II G2-3, radiotherapy is given with **54 Gy**, 1.8 Gy daily fractions.

IRS group III (macroscopic residual disease at initial resection):
As for synovial sarcoma, after the initial 3 cycles of chemotherapy, tumour-reassessment and then local treatment need to be planned.
a. Patients with the option of secondary complete resection:
Patients with initially unresectable tumour are at high risk of local failure. In the St. Jude's experience, local failure rate was 44 % at 5 years (*Spunt S, 2002*.). The mainstay of treatment is to obtain a secondary complete resection. Initial incomplete resection should be followed by immediate re-resection if expected to be complete and non-mutilating. In all other patients, chemotherapy is administered before second surgery is attempted. The use of radiotherapy is a matter of debate in patients with secondary complete resection. In the paediatric series from the INT Milan, the 5-year OS of the 40 group III patients was 52%, and correlated with the chance to undergo delayed surgery with histologically free margins. No major differences were observed according to the administration of post-operative radiotherapy: 5-year OS was 80% in the 11 patients who had delayed complete surgery alone, and 86% in the 8 patients who had delayed complete surgery followed by radiotherapy (*Ferrari A, J Clin Oncol 2005*).
Similarly to IRS group III synovial sarcomas, there is no a consensus about a common approach concerning radiotherapy, in particular on:
1) the necessity to give radiotherapy after delayed complete surgery
2) what is the best option, when the decision to give radiotherapy has been taken, between preoperative
and post-operative radiotherapy
(pre-operative irradiation can improve the chance to perform a complete secondary resection; moreover, pre-operative radiotherapy could be more effective in non-hypoxic tissues, may reduce the risk of intra-operative contamination, and could use smaller radiotherapy fields; post-operative radiotherapy has a small risk of wound complication).
Therefore, there are three treatment options for patients with the option of secondary complete resection:
a1. Preoperative RXT with **50.4 Gy** in 1.8 Gy daily fractions
a2. No additional RXT following secondary complete resection
a3. Postoperative RXT with **50.4 Gy** in 1.8 Gy daily fraction
The decision may depend also to the physician's preference.
However, possible suggestions are:
- to avoid RXT in younger patients after delayed complete surgery (< 6 years)
- to give RXT in case of initial large tumour size (> 10 cm) and in case on first surgical approach (biopsy) that could have caused tissue contamination.
The results of the different local modality groups will be compared
a.4 Following secondary incomplete resection, **54 Gy** have to be given with microscopical residual disease. In case of macroscopic residual disease, radiotherapy has to be given according to patients with no second surgery (see below)

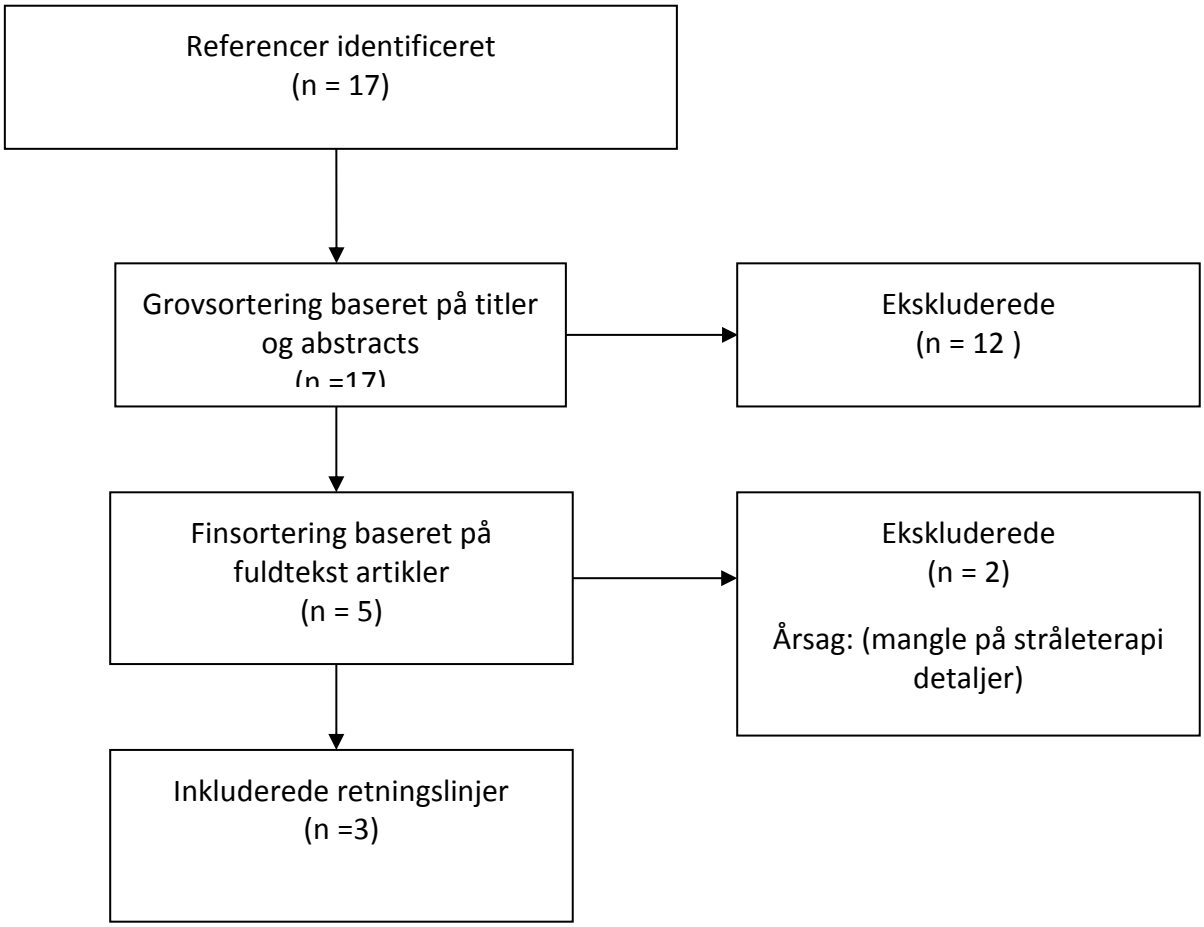
b. Patients without the option of secondary complete resection:
Radiotherapy is then the only local therapy modality and should be given with high doses. The recommended dose is **59.4 Gy**. An additional boost of 5.4 Gy can be given when there is residual disease at the end of radiotherapy. The dose recommendation may need modification depending on the age of the patient and the tumour site.
►►► Timing of radiotherapy
IRS group I (> 5 cm) and group II:
Radiotherapy (when indicated) should start after 3 cycles of chemotherapy. Radiotherapy plans

should be performed during the 7° week, with the aim to start the irradiation at **week 9**, at the resolution of the toxicity of the third cycle of chemotherapy.
During the administration of radiotherapy (5-6 weeks, overlapping with 2 chemotherapy cycles) chemotherapy will be given with ifosfamide alone.
IRS group III:
The option for second surgery must be checked before the onset of radiotherapy.
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:
- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy

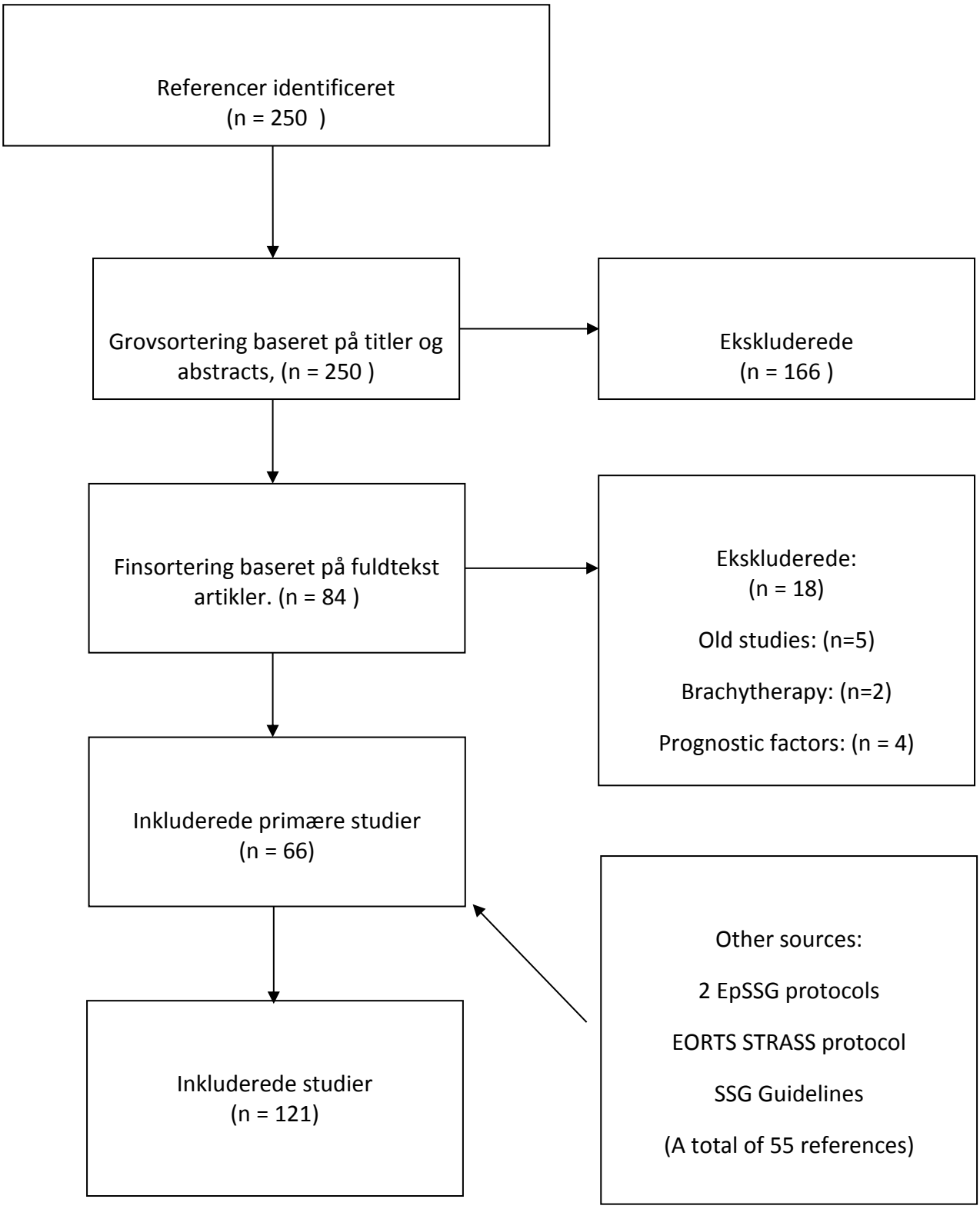
When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy to avoid surgical complications. The sixth cycle of chemotherapy should be given after the end of radiotherapy and before surgery, the last cycle after surgery.
When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.
►►► Radiotherapy in younger children
Children < 3 years of age
IRS group I independent of size: no RXT
IRS group II G1: no RXT
IRS group II G2 and G3: 50.4 Gy
IRS group III and delayed complete resection no RXT
IRS group III, no second surgery possible: 50.4 Gy

Appendix 4 – Flow chart

Flowchart – Guidelines



Flowchart – Primære studier



Appendix 5 – Evidence table

	DSG	Retningslinjens emne/titel: Radiotherapy of localised soft tissue sarcoma							
Ref. Nr.	***Forfatter/ kilde***	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
1	Gerner RE et al.	1975	retrospective	2b	surgery	amputation vs. local therapy	limb	Amputation gives better local control	155 pt.
2	Lindberg RD et al.	1981	retrospective	2b	surgery + postop. Rth		all sites	Good local control	300 pts
3	Rosenberg SA Et al.	1982	prospective	1b	surgery and radiotherapy	amputation vs. local surgery + Rth	limb	Equal results of the 2 strategies	43
4	Yang et al.	1998	prospective	1b	LSS + surgery vs. surgery	LC	limb	Rth improve LC but not OS	141 both high (91) and low grade (50)
5	Beane JD et al.	2014	prospective	1b	adj. rth	surgery vs. surgery + rth	limb	Rth improve local control	No survival benefit, 141 pts
6	Pisters PW	199	prospective	1b	adj. Rth	Surger vs.	limb and trunk	Rth improves	164 pts.

	et al	6				surgery + rth		local control	Brachytherapy
7	Harrison LB et al.	1993	prospective	1b	adj. rth	Surgery vs. surgery + rth	limb and trunk	Rth gives durable local control	126 pt. Brachytherapy
8	Italiano A	2014	database	2c	adj therapy		all sites	Rth improves local control	3255 pts
9	Jebsen NL et al.	2008	database	2c	adj. rth		trunk and limb	Rth imrove LC	1093
10	Casali PG et al.	2018	guidelines	2c	adj. Rth		all sites		ESMO
11	Rydholm A	1991	retrospective	2b	superficial STS	surgery ± Rth	limb abd trunk	Rth could be omitted	129
12	Tsagozis P et al	2015	database	2c	superficial STS	Surgery ± Rth	limb and trunk	Surgery is 1.ry ttt	622
13	Larrier NA et al	2016	review	2b	superficial and deep	Surgery and Rth	all sites		
14	Strander H et al	2003	review	2b	superficial and deep	Surgery and Rth	all sites		4579
15	Pisters PW	2007	review	2b	superficial and deep	Surgery and rth and cth	all sites		
16	Alektiar KM et al.	2000	retrospective	2b	+ve margin	LC	limb	Rth improve LC but inferior to –ve margin	110
17	Tang YW et al.	2012	retrospective	2b		Margins & recurrence	all sites	Rth is not substitute for surgery	73 pts
18	Choong PF	200	retrospective	2b	low grade	LC	limb	Rth for close	132

	et al.	1						margin	
19	Mollabashy A	2002	retrospective	2b	post op for low grade	LC	limb	No effect of Rth	108
20	Pisters PW et al.	2007	prospective	2b	Selective Rth	LC	limb and trunk	Rth for selected cases	88
21	Schreiber D et al.	2012	database	2c			limbs	Rth improve survival in T. >5cm	983 pts
22	Alektiar KM et al.	2002	retrospective	2b	<5cm	LC	limb	No effect of rth	204
23	Kepka L et al.	2005	retrospective	2b	radical rth.		all sites	Effective LC	112 pts
24	Weber DC et al.	2007	retrospective	2b	proton		parameningeal RMS	Good LC	39 pts
25	O'Sullivan B	2002	prospective	1b	pre vs. post	LC	limb	Pre = post	190
26	Davis AM et al.	2002	prospective	1b	pre vs. post	LC, physical function	limb	Pre = post	190 pts
27	Davis AM et al.	2005	prospective	1b	pre vs. post op.	Late effects	limb	More late effects with postop.	129 pts
28	Al-Absi E	2010	review	2b	preop. rth	LC & mets rate	limb	Preop. Is safe and effective	1098
29	Sampath S et al.	2011	retrospective	2b		Pre vs. post	all sites	Better OS for preop.	821
30	Zagars GK et al.	2003	retrospective	2b	sequencing in reexcision	LC	all sites	Pre or post op. rth is possible	295

								with reexcision	
31	Dagan R et al.	2012	retrospective	2b	preoperative rth		limb	Margina margin is enough	317 pts
32	Alamanda VK et al.	2014	retrospective	2b		Boost vs. no boost	limb	No effect of boost	94 pts
33	Al Yami A et al.	2010	retrospective	2b			positive margin	No advantage of boost	216 pts
34	Fourquet J, et al.	2016	retrospective	2b	time interval	Different intervals	STS	Interval doesn't affect outcome	1131 pts
35	Merimsky O, et al.	2005	retrospective	2b	Post-op.		limb	feasible	133 pts
36	Ballo MT, et al.	2004	retrospective	2b	interval	LC		Interval didn't impact LC	799 pts.
37	Schwartz DL, et al	2002	retrospective	2b	delay in post op.	LC	trunck and limb	Inferior results in >4 months	102
38	Julie Chu et al.	2013	guidelines	A	evidence based	LC and survival	All sites	Preoperative dose	australian
39	Jebsen NL et al.	2015	guidelines	A	evidence based	LC and survival	All sites	Preoperative dose	scandinavian
40	NCCN	2018	guidelines	A	Evidence based	LC and survival	All sites	Preoperative dose	amedican
41	Pollack A, et al.	1998	retrospective	3b	Pre and post op. rth	LC	All sites	50 Gy post op. is not enough. Individual selection for pre	453

								or post	
42	Jebsen NL, et al.	2013	retrospective	2b	Postoperative dose	LC	Trunk and limb	No dose reposne	462
43	Levy A, et al.	2018	retrospective	2b	Postop rth	Different doses	Limb STS	Dose escalayion is safe	Dose determined by expert MDT
44	Zagars GK, et al.	2003	retrospective	2b	Post op. dose	LC	All sites	Better LC with doses>60 Gy for high risk	775 pts.
45	Wolfson AH, et al.	1998	retrospective	3b	Dose response	survival	limb	Better survival with higher dose	59 pts
46	Dinges S et al	1994	retrospective	3b	Post op. dose	LC	All sites	Better LC with doses>60 Gy	102
47	Delaney TF, et al.	2007	retrospective	2b	+ve margin		All sites	>64 Gy for +ve margin	154
48	Kubicek GJ, etal.	2018	Phase II	2b	Preop-hypo-fractionation		STS different sites	Radiosurgery is well tolerated	13 pts
49	Raval RR, etal.	2017	retrospective	3b	Cth + split course Rth		STS all sites	Split course + cth is effective	Only 16 pts
50	Soyfer V, et al.	2013	retrospective	3b	Hypo-fractionation		elderly	Hypofractionation is feasible	21 pts
51	Le Pechoux C, et al.	1999	retrospective	3b	hyperfractionation	LC	limb	Hyperfractionation is effective	62
52	Mundt AJ,	199	retrospective	2b	Margin to CTV	LC	limb	5cm margin is	64

	et al.	5						adequate	
53	Kim B, et al	2010	retrospective	2b			Target definition		56 pts
54	Dickie CI	2012	retrosåpective	2b	Target volume	LC	Target definition	Recurrence in field	60 pts
55	Choi N et al.	2018	retrospective	2b	Post.op rth		Lower limb	Local recurrence in or close to Fluid collection	88 pt
56	Baldini EH et al	2015	guidelines	3b	Preop rth			Expert panel	
57	Tiong SS et al	2016	review	3b	role of rth	LC	All sites		
58	Haas et al	2016	review	3b	role of rth	LC	limb		
59	O'Sullivan B, et al.	2013	Phase 2	2b	IG-IMRT		limb	IG-IMRT reduce tissue transfer	70 pts
60	Alektiar KM, et al.	2007	retrospective	3b	IMRT		limb	IMRT give excellent LC	31 pts.
61	Alektiar KM, et al.	2008	retrospective	3b	IMRT		limb	IMRT give excellent LC	41 pts.
62	Lin C, et al	2012	Prospective, single arm	2b	IMRT		All sited	Better sparing of normal tissue	375 pts, Rhabdomyosarcoma
63	Stewart AJ et al	2009	retrospective	3b	IMRT post op.		limb	Better target coverage	10 pts.
64	Folkert MR,	201	retrospective	2b		IMRT vs.	Limb STS	Less recurrence	Good study 319

	et al.	4				conventional		in IMRT	pts
65	Wang D, et al.	2015	Phase II	2b	IGRT	Compared with historical data	limbs	IGRT reduce late effects	No marginal failures
66	Smith KB et al	2011	retrospective	3b	Definitive Rth			Local failure is fatal	Non RMS, children and young adults
67	van Dalen T et al.	2007	retrospective	2b	Surgery	LC and survival	retroperitoneal		143 ots
68	Cosper PF et al	2017	retrospective	2b	IMRT perioprtauive	LC	retroperitoneal	Excellent control	30 pts
69	Pawlik TM, et al.	2006	prospective	2b	Pre-op.	historical	retroperitonium	Pre-op. gives better LC end hisorical	72
70	Kepka L et al	2012	retrospective	3b	Definitive rth	LC	Limb and retroperitoneal	Good control. Rth should be considered	112
71	Zlotecki RA, et al.	2005	retrospective	3b	Pre. vs. post op.	LC-complications	retroperitonium	Rth improve LC. Preop is better	40 pts.
72	Catton CN, et al.	1994	retrospective	2b	104	LC	retroperitonium	Post op.rth dose of >35 Gy give longer PFS	104
73	Green WR, et al.	2018	database	2c	Adj. Rth		Non-retroperitoneal sarcoma	Adj. Rth improves OS in high grade pts	2832 pts
74	Reed NS et al	2008	Prospective phase III	1b	Adj rth vs. surgery	LC	Uterine sarcoma	No survival difference	224 pts
75	Sampath S et al	2010	retrospective	2c	Adj rth	LC	Uterine sarcoma	Rth imrpve LC	2206 pts
76	Terek MC	201	retrospective	2b	Adj rth	LC	Uterine sarcoma	Rth imrpve LC	57 pts

	et al	6							
77	Magnuson WJ et al	2015	retrospective	2b	Adj rth	LC	Uterine sarcoma	Rth imrpve LC in stage I	157 pts
78	Sampath S and Gaffney DK	2011	review	2b	Role of rth	LC	Uterine sarcoma		
79	Livi L et al	2003	retrospective	2b	Role of rth	LC	Uerine sarcoma	Rth is indicated in stage I-III	141 pts
80	Le T	2001	retrospective	2b	Role of rth	LC	Uterine carcinosarcoma		32 pts
81	Ferrer F et al	1999	retrospective	2b	Adj rth	LC	Uterine sarcoma	Rth improve LC and PFS	103 pts
82	Yu T et al	2015	retrospective	2b	Adj rth	LC	Uterine sarcoma	Rth improve LC and PFS	75 pts
83	Weitmann HD et al	2001	retrospective	2b	Adj rth	LC	Uterine stromal sarcoma	Rth improve LC and PFS	21 pts
84	Malouf GG et al	2013	retrospective	2b	Role of rth	LC	Uterine sarcoma	Combined ttt strategy	29 pts
85	Philip CA et al	2014	review	2b	Role of rth	LC	Uterine sarcoma	Combined ttt strategy	
86	Linthout N et al.	2006	review	2b	Technical note				
87	Mahmoud O, et al.	2017	database	2c	Adj.rth		Head and neck STS	Adj Rth improves survival	788
88	Orbach D, etal.	2017	retrospective	2b	Adj.rth		H&N non-parameningeal RMS	Adj. improves survival and LC	140 (children)

89	Minard-Colin V, et al.	*2013*	*retrospective*	*2b*	*Cth+Rth+surgery*		*Head & neck sarcoma*	*Surgery + Rth is better than Rth alone*	*41 pts also children*
90	O'Sullivan B, et al.	2003	retrospective	3b	preop	LC	Head and neck	Less wound complication than limb and goos control	40 pts
91	Jang JH, et al	2012	retrospective	2b	surgery	LC	Breast phylloides sarcoma	Margin determine local recurrence rate	164
92	Barth RJ	1999	review	2b	surgery	LC	Breast phylloides	High recurrence rate with surgery alone	
93	Barth RJ et al.	2009	prospective	2b	Surgery + adj. rth	LC	Breast phylloides	Less recurrence after rth	46
94	Belkacemi Y et al	2008	retrospective	2b	Adj. rth	LC	Breast phylloides	Rth should be considered for high risk	443
95	Gnerlich JL et al	2014	database	2b	Adj rth	LC	Breast phylloides	Rth should be considered for high risk	3120
96	Kim YJ, and Kim K	2017	database	2b	Surgery + adj. rth	LC	Breast phylloides	Rth should be considered for high risk	1974
97	Ghareeb ER et al	2016	retrospective	2b	Surgery + adj. rth	LC	Breast angiosarcoma	Less recurrence after rth	35
98	Luini A et al	2007	review	2b	Surgery + adj. rth	LC	Breast angiosarcoma	Less recurrence after rth	
99	McGowan	200	retrospective	2b	Surgery + adj.	LC	Breast sarcoma	Rth for microscopic	32

	TS et al	0			rth			disease	
100	Barrow BJ, et al.	1999	retrospective	3b	Role of rth	LC	breast		59
101	Wolden S et al	1999	prospective	1b	Risk adapted combined tt	LC and survival	All sites		439 pts
102	Schuck A, et al.	2004	Prospective	1b	indication	LC	All sites	RTh is indicated in group II RMS	203
103	Arndt C et al	2001	Prospective	1b	indication	LC	Gynecolocial sites	RTh improves outcome	151
104	Martelli H et al	1999	Prospective	1b	indication	LC	Gynecolocial sites	RTh improve LC	38
105	Koscielniak E et al	2002	review	1b	indication	LC	all sites	RTh is indicated high and intermediate risk	
106	Regine WF et al	1995	Prospective	1b	Radiation dose	LC	all sites	At least 40 Gy	103
107	Donaldson SS, et al.	*2001*	*prospective*	*1b*	*Hyperfractionation*	*Hyperfractionation vs. conventional Rth*	*Rhabdomyosarcoma*	*Hyperfractionation is as effective as conventional*	*Also children,* *559 pts*
108	Oberlin O et al	2001	*prospective*	*1b*	*indication*	*LC and survival*	*Orbital RMS*	*Subset may not need rth*	*306*
109	Schuck A et al	2004	*prospective*	*1b*	*indication*	*LC and survival*	*All sites*	*Rth improves results of group II*	203
110	Koscielniak E et al	2002	review	1b	indication	LC	all sites	RTh is indicated in group II RMS	
111	Suit H et al	200	review	2b					

		8							
112	Miralbell R et al	2002	Case report/review	c	*indication*		Children all sites	normal tissue dose sparing advantage	2 pts
113	Hug EB et al	2000	Case report/review	c	*indication*		Children all site	normal tissue dose sparing advantage	2 pts
114	Weber DC et al	2004	Case report/review	c	*indication*		Children all site	normal tissue dose sparing advantage	5 pts
115	DeLaney TF et al	2009	Phase II	3b	*indication*	LC	Spine sarcoma	High LC	50 pts
116	Guttmann DM, et al.	2017	retrospective	2b	Re-irradiation		2ry or recurrent STS	Proton is safe as reirradiation	26 pts
117	Weber DC et al	2007	retrospective	2b	*indication*	LC	sarcomas	Spot scanning is effective and safe	13
118	Ladra MM et al	2014	retrospective	2b	*indication*	LC	Pediatric RMS	Lower integral dose	54 pts
119	Ladra MM et al	2014	Phase II	2b	*indication*	LC and survival	Pediatric RMS	Good LC and survival	57 pts
120	Childs SK et al	2012	retrospective	2b	*indication*	LC	Parameningeal pediatric RMS	Good LC	17 ptas
121	Cotter SE et al	2012	retrospective	3b	*indication*	LC	Bladder/prostate RMS	Dose saving	7 pts
122	Timmermann B et al	2007	retrospective	3b	*indication*	LC	Pediatric sarcoma	Good LC	16 pts

123	Greiner R et al	1990	retrospective	3b	*indication*	LC	sarcomas	Spot scanning is feasible	35 pts
124	Nowakowski VA, et al.	1992	retrospective	2b	proton	LC	paraspinal	Feasible to delriver high dose	52 (14 sts)